”BABEȘ-BOLYAI” UNIVERSITY, CLUJ-NAPOCA

FACULTY OF BIOLOGY AND GEOLOGY

Doctoral School: *Integrative Biology*

Ph.D. THESIS

SUMMARY

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Cluj-Napoca

2020

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PROTEINS AND PLANT EXTRACTS STUDIED WITH EXPERIMENTAL MODELS OF OXIDATIVE STRESS

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”*What we observed is not nature itself,*

but nature exposed to our method of questioning”

Werner Heisnberg

1925

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ABBREVIATIONS

3-NT - 3-nitrotyrosine

AA - adrenalin

ABTS - 2,2'-azino-bis(3-etilbenzotiazolin-6-sulfonic) acid

AchE - acetylcholinesterase

AgNP - silver nanoparticles

AIF - apoptosis inducing factor

ALB - albumin

ALT - alanine aminotransferase

ANOVA - Analysis of Variance

APO-1 - anti-Fas monoclonal antibody

aPTT - tromboplastine partial activated time

APZ - alprazolam

ARE - Antioxidant Response Elements

ASME - acetyl-shanshizide-methylester

AST - aspartate aminotransferase

ATPază - adenozine triphosphatase

BAD - Bcl-2 associated death promoter

BAX - Bcl-2 Associated Protein X

Bcl-2 - B cell lymphoma-2

Bcl-X_L - B-cell lymphoma-extra large

BCR - B cell receptor

BE (b) - base excess (buffer)

BE (ecf) - base excess (extracelullar fluids)

BID - BH3 interacting-domain death agonist

BSA - bovine serum albumin

BuChE - butyrylcholinesterase

C3C - C3 complement

CA3 (aria) - hippocampal area no. 3

CaCo2 - colorectal adenocarcinoma cells

CAT - catalase

CD19 - B-lymphocyte antigen CD19

CHOL - cholesterol

CMC - carboxymethylcellulose

Colec12 - scavenger receptor with C-type lectin domain

COX-2 - cyclooxigenase 2

CREA - creatinin

CRH - corticotropin releasing hormone

CRP - C reactive protein

CS - corticosterone

CT-26 - colon carcinoma cells CT-26

Cullin-3 - Cullin-RING E3 ubiquitin-ligase, protein complex

CyOx - cytochromoxidase

DADS - diallyldisulfide

DAS - diallylsulfide

DATS - diallyltrisulfide

DPPH - 2,2-diphenyl-1-pycrylhydrazyl

DTNB - ditionitrobenzoic acid

$EDTAK_2$ - ethylendiaminoteratracetic acid dipotassium salt

ELISA - enzyme-linked immunosorbent assay

EndoG - endonuclease G

eNOS - endothelial NO sintase

ERK ½ - extracellular signal-regulated kinase 1/2

FADD - Fas-associated protein with death domain

Fas - apoptosis 1 antigen (APO-1)

FDU - human dermic fibroblasts

FG-7142 - N-methyl-9H-pyrido[5,4-b]indole-3-carboxamide

GABA - gama-aminobutiric acid

GL - glutaraldehyde

GLP-1 - glucagon-like peptide 1

GLP-1R - glucagon-like peptide 1 receptor

GLUC - glucose

GOT - glutamate-oxalate transferase

GPT - glutamate-pyruvate transferase

GPX - glutathione peroxidase

GRA - granulocytes

GRA% - granulocytes %

GSH - glutathione reduced

Hb - hemoglobin

HCT - hematocrit

HDL - high density lipoproteins

HE - hematoxylin - eosine

HepG2 - HepG2 hepatoblastoma cells

HGB - hemoglobin (in Complete Blood Analysis)

HHHS - hippocampus - hypothalamus - pituitary - adrenals axis

HPLC - high performance liquid cromatohraphy

Hr - hemerythrin

HSA - human serum albumin

HSV - *Herpes simplex* virus

IC_{50} - cytotoxicity index (for 50% of the cells)

IFN - interferone

IgA - immunoglobulin A

IgG - immunoglobulin G

IgM - immunoglobulin M

IL-1α - interleukin 1α

IL-1β - interleukin 1β

IL-6 - interleukin 6

IL-8 - interleukin 8

iNOS - NO sintase inducible

JNK - Janus kinase

kDa - kiloDaltons

Keap1 - Kelch like - ECH - associated protein 1

LDL - low denisity lipoproteins

LYM - limphocytes

LYM% - limphocytes %

LYN - tyrosine kinase LYN

Maf - proto - oncogene C - masculoaponeurotic fibrosarcoma

MAO - monoamine oxidase

MARCO - macrophage receptor with collagenous structure

MCF-7 - MCF-7 lung carcinoma cells

MCH - medium cellular hemoglobin

MCP-1- monocyte chemoattractant protein 1

MCV - medium cellular volume

MDA - malondialdehyde

MDBK - Madin-Darby Bovine Kidney cells

metHb - met-hemoglobin (Fe^{3+})

MIP - MIP - macrophage inflammatory protein

MON - monocytes

MON% - monocytes %

Msr1 - macrophage scavenger receptor 1

NAD(P)H - nicotinamid adenin-dinucletide phosphate reduced

NEU - neutrophils

NEU% - neutrophils %

NF-κβ - nuclear factor κβ

NO - nitrogen monoxide

NOS - nitrogen reactive species

NPV - paraventricular hypothalamic nucleus

Nrf2 - nuclear factor (erythroid-derived 2)-like 2

NROR - NADH/rubredoxin oxidoreductase from *Clostridium acetobutylicum*

oATP - ATP oxidized

oxyHb - oxyhemoglobin (Fe^{2+})

p38 - MAPK - p38 mitogen-activated protein kinases

p53 - proteina p53

pAkt - phosphorilated proteinkinase B

PBS - phosphate buffer saline

PC-3 - human prostate cancer cells

PCA - Principal Component Analysis

PCT - platelets proportion in total blood

PET - polyethylenglycol

PI3K - phosphatidylinositol-3-kinase

PKB - proteinkinase B

PLT - platelets

pNF-κβ - nuclear factor κβ activated

PT - prothrombin time

PUFA - polyunsaturated fatty acids

RANTES - regulated on activation normal T cell expressed and secreted

RBC - red blood cells

Rbr - rubrerythrin

RMN - magnetic and nuclear resonance

ROS - reactive oxygen species

RT-PCR - real-time PCR (polymerase chain reaction)

SAC - S-allyl-cysteine

SAMG - S allyl-mercaptoglutathione

SCAR B1 - scavenger receptor class B type 1

SCAR B2 - scavenger receptor class B type 2

SD - standard deviation

SDS - sodium dodecylsulphate

SEM - standard error of the mean

SH - thiol group

SKOV 3 - ovarian cancer cells from ascite liquid

SME - shanshiside-methyl ester

SYK - SYK tyrosinase

TBARS - thiobarbituric acid reactive species

TGL - tryglicerides

TGO - glutatate-oxalate transaminase

TGP - glutamate - pyruvate transaminase

THCB - tetrahydrocarboline

TNFα - tumor necrosis factor α

TP - total proteins

Trolox - 6-hydroxy-2,5,7,8-tetramethylcroman-2-carboxylic acid

TUNEL - terminal deoxynucleotidyl transferase dUTP nick end labeling

UDP - uridine diphosphate

UREA - urea

UV-vis - utraviolet - visibile

VADC - voltage-dependent anionic channel

VEGF - vein endothelial growth factor

WBC - leucocytes

β - HT_2 - serotonin receptor type β

Introduction

The general purpose of this Ph.D. thesis was to identify common elements existing between different applications of an in vivo experimental model and to investigate the reactivity of the biosystem used in correlation with the activity of some biomolecules tested in terms of the dynamics of oxidative stress, immune reaction and specific morphological changes (cerebral, glandular, hepatic, renal). The experimental model used was applied to the white rat of the Wistar breed, exposed to different inducing factors of metabolic imbalances. In these experimentally generated situations, the bioactivity of some proxy proteins (hemoglobin, hemerythrin), some plant compounds such as allicin or curcumin and plant extracts of *Lamium*, *Galium*, *Cornus*, *Vaccinium*, *Malus*, and *Hypericum* were evaluated. The experimental data obtained outline the area in which a biosystem reacts under experimental conditions, the nitro-oxidative stress being an extremely dynamic indicator of the metabolic processes pursued.

Research objectives

The objectives of the research were: (i) to investigate the action of proteins such as hemoglobin (Hb) and hemerythrin (Hr), together with their derivatized products and systemic reactivity in terms of nitro-oxidative stress, immune reaction and histopathological changes; (ii) testing the in vivo activity of molecules such as allicin, in order to establish the mechanism by which it stimulates humoral-mediated immunity and curcumin, in order to evaluate the neuroprotective action via ERK1 / 2-NF-kβ under the conditions of the cognitive disorder induced by diazepam; (iii) the evaluation of the bioactivity of some plant extracts in different pathological conditions induced with xenobiotics in terms of the nitro-oxidative stress as well as the effect on some main metabolic parameters and the histopathological evaluation; (iv) the research of the biology and pathology of the nitro-oxidative stress at the level of the central nervous system, induced by restraint stress, frequently used as an experimental disruptive factor of the neuroendocrine system.

THEORETICAL FUNDAMENTALS

1. THE EXPERIMENTAL MODEL

1.1. The experimental model in biology and medicine

All analytical sciences use decomposition to experiment better. The reduction of all vital manifestations of the complex organism to the functions of several organs, and their action on the properties of tissues, cells or ultrastructural elements, as Claude Bernard states, is the mandatory way for the experimental research of a complex organism. Experimental analysis decomposes complex phenomena into increasingly simple phenomena until it reduces them if it is possible to only two elementary conditions necessary for the occurrence of the phenomenon (Bernard, 1958; Arendt, 2018). Thus, we define the experimental model, in biology and

medicine, as a system under the influence of as many external factors in which the studied phenomenon is reduced to a high degree of simplification and correlated with its nature, the main purpose being to know the law of the phenomenon studied.

1.2. Method, model, models system

Life research, which is structured on organic and inorganic components and governed by the laws of nature, requires the use of (i) physico-chemical (pH, spectrophotometry, MRI), (ii) biochemical (ELISA, immunohistochemistry, immunochemistry) and (iii) biological methods (including the first two categories) such as histopathological, ultrastructural or functional analysis methods. The integration of the methods for the study of the behavior, specific to other specialized areas (psychology, psychiatry) leads to an interdisciplinary research and to the possibility of evaluating several experimental models within the same individual, thus talking about systems of experimental models. The induction of an autism-specific prenatal neuropathology (biological model with sodium valproate) leads for example to a system of experimental models, on the one hand the model for autism (includes behavioral evaluation) and on the other, the biological model for liver fibrosis (morphologically and biochemically evaluated.

1.3. Multidimensional experimental models

The physiological processes, by their complexity, require several angles from which to be approached both in order to understand them, as well as the bioactivity of molecules with therapeutic, adjuvant or prophylactic potential interposed in the range of metabolic and behavioral reactions. Therefore, the multidimensional experimental model represents the biological model for a given phenomenon, approached from an interdisciplinary perspective, the same biosystem being evaluated both from a biochemical and morphological point of view, as well as a functional or behavioral one. By functional evaluation, we mean the set of measurements that include blood pressure, heart rate, myocardial, cerebral or muscular electrical function, MRI imaging elements or echographic aspects.

2. EXPERIMENTAL MODELS ON WISTAR RAT FOR THE STUDY OF THE BIOLOGY AND PATHOLOGY OF THE NITROOXIDATIVE STRESS

Hemoglobin (Hb) (**Fig. 1a**) is a tetrameric protein, with a role in the transport of O_2, CO_2, NO, consisting of a protein group, globin, and a prosthetic group, the heme, which contains an iron atom coupled to the porphyrin ring (Reeder and Wilson, 2005). Iron is a redox-active metal with variable valence, thus supporting a series of both self-oxidation and free radical generation reactions (Scurtu et al., 2013). When hemic iron is in a low state (ferrous, Fe^{2+}), the oxygen binding and transport by hemoglobin are possible. However, as Reeder and Wilson (2005), Scurtu et al. (2013), Rifkind et al. (2015) or Kock et al. (2016) demonstrate, molecular

oxygen being a pro-oxidant, determines the oxidation of Fe^{2+} (oxyHb) to Fe^{3+} (metHb) and transformation of hemoglobin into methemoglobin, the reaction also generating superoxide O_2^-, hydroxyl, but also peroxide (from superoxide degradation) radicals. Hemerythrin (**Fig. 1b**) is a nonheminic cytoplasmic protein with two iron atoms (Fe^{2+} - Fe^{2+}) that carries respiratory gases (Scurtu et al., 2013). The current data demonstrate the presence of genomic sequences corresponding to hemerythrin in the archea (3), bacteria (118) and eukaryotes (fungi, cnidarians, annelids) and absence in the deuterostome ancestors (Bailly et al., 2008). Hemerythrin does not react with hydrogen peroxide, NO and nitrite (Moţ et al., 2010; Scurtu et al., 2013; Hathazi et al., 2014). Experimental data suggest that hemerythrin does not generate oxidative stress or, if involved in its generation, the role of this protein is secondary, as the oxidative stress generated is the consequence of the immune reaction that hemerythrin activates (Toma et al., 2018).

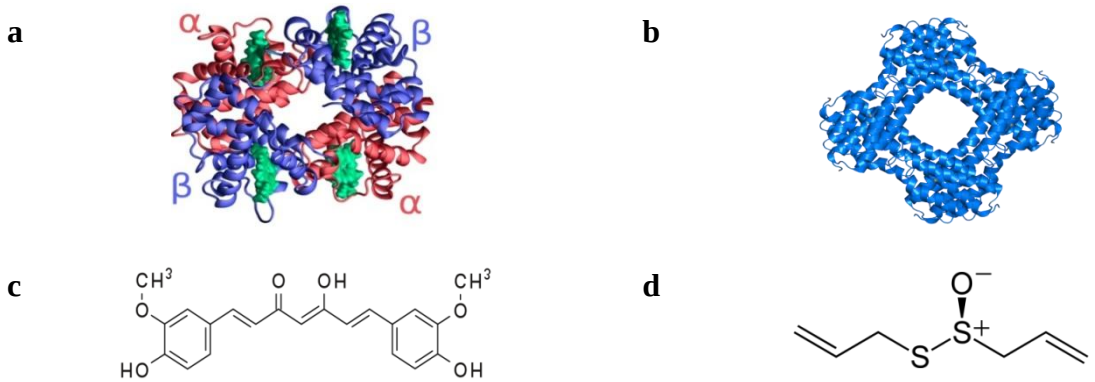

Fig. 1. The tetrameric structure of Hb (after Bringas et al., 2017) (a), the homo-octameric structure of Hr (PDB) (b), the structure of curcumin (PubChem) (c) and allicin (PubChem) (d). The pro-oxidant or antioxidant action of Hb, Hr, curcumin or allicin is due to the mechanisms by which these molecules can generate free radicals (Hb, Hr), can also generate free radicals (curcumin) or can only capture free radicals such as allicin.

Between the nitro-oxidative stress and the immune reaction, there is an inverse proportional correlation specific to the cellular redox status of the moment when the biological sample is taken (Lee et al., 2015; Toma et al., 2019) for biochemical determinations. Experimental models for specific ambivalent (humoral and cellular) immunostimulation and nitro-oxidative stress are therefore complemented by the model for exposure of the biosystem to Hb or Hr administered intravenously (between them being net differences in terms of free radical generation).

2.2. Plant compounds with antioxidant, immunomodulatory and/or neuroprotective action

Curcumina este un polifenol vegetal (**Fig. 1c**) cu multiple bioactivități printre care se numără efecte hipoglicemiante, hipolipemiante, anxiolitice, neurotrofice, antineoplazice, adjuvante în sindromul metabolic, antifungice, antibacteriene, antiinflamatoare și antioxidante după cum arată numeroase date din literatură (Maheshwari și colab., 2006; Jurenka, 2009; Noorafshan și Ashkani-Esfahani, 2013; Hewlings și Kalman, 2017). Alicina activează calea de

semnalizare *Nrf2-Keap1-ARE* (Li şi colab., 2012; Xu şi colab., 2014; Borlinghaus şi colab., 2014). Nrf2 (Nuclear factor (erythroid-derived 2)-like 2) este un factor de transcriere codificat de o genă omoloagă, fiind sub aspect structural o proteină pe motivul fermoarului leucinic (**Fig. 3**), ca majoritatea factorilor de transcriere însă de tipul Bzip (basic leucine zipper), motiv bine conservat de-a lungul evoluţiei (Entrez Gene Nuclear factor erythroid-derived 2 - like 2).

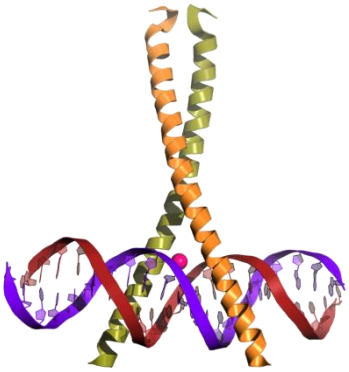

Fig. 3. 3D structure of how the leucine zipper interacts with DNA (Ellenberger, 1994).

Based on these two mechanisms, there are four possible reaction pathways through which phenolic, amine or ketone antioxidants exert their properties: (i) disruption of chain oxidation (phenols, hydroquinones); (ii) deactivation of some metal ions (salicylenediamines); (iii) deactivators of UV radiation (aromatic ketones) and (iv) decomposition of peroxides (butyrates, benzylamine) (Robak and Gryglewski, 1988; Ricardo da Silva et al., 1991). The immunostimulatory action of the compounds of plant origin is non-specific (Toma et al., 2019) and leads to the stimulation of cellular and / or humoral mediated immunity, the latter being predominant. As shown by a consistent body of work (Wagner et al., 1999; Kanan et al., 2007; Archana et al., 2011; Breyer et al., 2015; Salehi et al., 2019), some plant extracts and compounds from plants have immunostimulatory properties marked by increased lymphocyte counts, stimulation of NK cell transformation, increased level of interleukins 1 and 2 (Liu et al., 2006), increased serum immunoglobulin concentration or indirectly, decreased oxidative stress and hormone concentration such as glucocorticoids (Rahimi et al., 2011).

2.3. Plant extracts with antioxidant properties and adjuvant/therapeutic action in experimentally induced pathologies

Pereira et al. (2013a, b) investigated the antioxidant and cytoprotective effects of purified ethanolic extracts of *Cytisus multiflorus*, *Lamium album* and *Thymus citriodorus*. These extracts exhibited prominent antioxidant activity, determined by the DPPH and Trolox method. Using a model for chemical stress, induced by potassium bichromate in HepG2 hepatoblastoma culture, a concentration of 50 µg / ml of *C. multiflorus*, *L. album*, and *T. citriodorus* extract decreased the rate of reactive oxygen species production (ROS) with 25%, 26% and 20% respectively, when exposed to 25 µM potassium bichromate. In addition, purified ethanolic extracts and prepared polyphenolic mixtures showed a cytoprotective effect against multiple toxicities

induced by potassium bichromate (Pereira et al., 2013a). Studies have shown strong antiviral action by blocking the replication of viruses. At the level of the urinary tract, by enteral administration, the extract of the meringue leaves has therapeutic effects in the case of nephritis, skin, cystitis. The main therapeutic action of the cranberry leaf extracts is the urinary antiseptic, manifested by the cleavage of the arbutoside and methylbutoside, from the leaves of the cranberries, in hydroquinone, respectively methyl-hydroquinone, which, together with flavonoids, imprints both urine and diuretic action on the extract. (Wilson et al., 1998; Terris et al., 2001; Liu et al., 2006). At the same time, for internal use, *G. verum* L. extract is used as a neuroprotective and adjuvant in antiepileptic therapy (Orhan et al., 2012; Tagarelli et al., 2013). Also, the extract of *G. verum* L. regulates blood circulation in the elderly and acts as a regulator of thyroid function (Roman and Puică, 2013; Roman et al., 2015; Bradic et al., 2018). For external use, *G. verum* L. preparations are astringent, healing, anti-inflammatory and antifungal (Mitic et al., 2014; Jan et al., 2015). Stojiljković et al. (2016) found that extracts of *M. sylvestris* Mill have therapeutic or adjuvant effects in high blood pressure (probably by eNOS stimulation), atherosclerosis, insulin-dependent diabetes, in rheumatic inflammation and in urinary infections (by possible action of urinary alkalinization). Research, often lacking, also shows a composition rich in polyphenols, tannins, anthocyanins (Kondo et al., 2002), rosmarinic acid, ursolic acid (Hagen et al., 2007), sinensitine, 3-hydroxy-tetramethoxy-flavone (Hossain et al., 2009), pectins, vitamin C and oligominerals (Rop et al., 2011). However, hypericin and hyperforin remain the specific compounds for *H. perforatum* L. and at the same time the compounds responsible for most of the pharmacotherapeutic properties of the species. In terms of the bioactivity of *H. perforatum* extracts, by far, the antidepressant and neurotrophic action (through the neuromodulatory and antioxidant properties) is the subject of most research related to this species. The anti-proliferative effect was also demonstrated by Tiptiri-Kourpeti et al. (2019) that exposed tumor cell lines, for 72h, at different concentrations of *C. mas* and *C. alba* extracts. The results showed that *C. mas* hydroalcoholic extract showed an antiproliferative effect on HepG2 lines of hepatocellular carcinoma and on CT26 colon carcinoma. *C. alba* extract had an antiproliferative effect on CaCo2 and HT-29 cell lines. The lung carcinoma of type MCF-7 was resistant to the action of fruit extract of *C. mas* respectively *C. alba*. However, further research has shown that *C. mas* extract had an antiproliferative effect on A549 large cell lung cancer, MCF-7 lung adenocarcinoma, SKOV 3 cell ovarian cancer, PC-3 prostate adenocarcinoma, in a dose-independent manner.

3. EXPERIMENTAL MODELS FOR THE STUDY OF THE NITROXIDATIVE STRESS BIOLOGY INDUCED BY WISTAR RAT EXPOSURE TO NEUROPSYCHOLOGICAL STRESS

3.1. Relation between neuropsychological stress and nitrooxidative stress

The stress, a term used in psychology, medicine, biology, and chemistry, broadly refers to the state or period of imbalance induced by a number of physical or chemical factors, of a system initially in equilibrium (homeostatic), in whose mechanisms new events occur (chemical, structural, behavioral reactions), leading to a series of modifications of that system, called adaptations (Brian, 1997; Chen et al., 2015; Toma et al., 2016). Events associated with increased blood levels of corticosteroids naturally leave behind free radicals that generate nitro-oxidative stress. The neuropsychic stress, which generates nitro-oxidative stress, is, therefore, firstly, a period of stimulation, which later becomes a period of degrading reactions producing energy, and in the end, to be associated with a number of adaptive morphological and biochemical reactions, as mentioned by Alkadhi (2013).

ORIGINAL CONTRIBUTIONS

4. SYSTEMIC REACTIVITY IN WISTAR RAT AFTER NATIVE AND DERIVATIZED HEMOGLOBIN AND HEMERYTHRIN EXPOSURE

4.1. Experimental design

The research was carried out on Wistar white rats, groups of 10 individuals, adult females, 24 weeks old, weighing 180 ± 30 g, F1 generation. The animals were obtained from the zoobase of the University of Medicine and Pharmacy "Iuliu Haţieganu" from Cluj-Napoca and grouped in experimental cohorts 12h before the experiment started. The maintenance of the experimental groups was carried out according to the Council Directive EU 2010/63 / EU and according to the Decision no. 1 / 28.02.2013 of the Ethics Commission of the Institute of Biological Research Cluj-Napoca, branch of the INCDSB Bucharest. The experiments and experimental procedures were carried out under appropriate zoo-hygienic conditions, in the biobased Faculty of Biology and Geology of the "Babeş-Bolyai" University of Cluj-Napoca, at a constant temperature of 20ºC, light / dark rhythm 12h / 12h. The diet of the animals consisted of the standard Cantacuzino pellet for small rodents, access to food and water being unrestricted. The experiments were of the acute type, lasting 24 hours, for both exposures to Hb and derivatives, as well as to Hr and its derivatives. Protein administration was injected intravenously into the vein, the volume injected being 0.2 mL/animal. All experimental groups (corresponding to each molecule tested) were compared with Control groups. Table 2 summarizes the types of derivatization products of Hb, respectively Hr and the general management framework of the obtained products, together with the summary of biological samples collected.

Tabel 2. The general schedule for the administration of derivatization products and native forms of Hb and Hr

Primer	Educts	mL adm.	Route of adm.	Reaction time	Samples
Hb	nHb	0.2 mL	intravenous	24h	whole blood, plasma, serum, liver, spleen kidney
	HbGL				
	HbBSA				
	HbRbr				
	HbRbrNROR				
	HboATP				
Hr	nHr	0.2 mL	intravenous	24h	whole blood, plasma, serum, liver, spleen kidney
	pHr				
	HrHSA				
	HrRbr				
Control		-	-	-	whole blood, plasma, serum, liver, spleen kidney

Caption: Hb - hemoglobin; Hr - hemerythrin; nHb - native hemoglobin; HbGL - hemoglobin polymerized with glutaraldehyde; HbBSA - hemoglobin copolymerized with BSA; HbRbr - hemoglobin copolymerized with Rbr; HbRbrNROR - hemoglobin copolymerized with Rbr and NROR; HboATP - hemoglobin copolimerized with oATP; nHr - native hemerythrin; pHr - hemerythrin polymerized with glutaraldehyde; HrHSA - hemerythrin copolimerized with HSA; HrRbr - hemerythrin copolymerized with Rbr.

5. OXIDATIVE STATUS AND BIOACTIVITIES OF THE CURCUMIN ON THE NERVOUS SYSTEM AND THE ALLICIN EFFECT ON THE IMMUNE SYSTEM IN WISTAR RAT

5.1. Experimental design

The research included two distinct experiments, both based on elements of oxidative stress. Curcumin was evaluated in terms of neuromodulatory effect, in the context of diazepam induction of redox imbalance, anxiety and memory disorders. Allicin was studied under normal conditions, markers of oxidative stress having physiological variations. **Table 15** summarizes the experimental groups, the treatments applied, the duration of the procedure and the type of tests, respectively of determinations performed. The evaluation of the bioactivity of allicin was based on an idea previously confirmed in the studies with Hb and HR. We aimed to isolate only the oxidative stress from the systemic inflammatory syndrome and then to act with antioxidant molecules such as allicin, in order to establish the correlations between the redox status and the immune reaction.

Tabel 15. Experimental design of curcumin and allicin testing under diazepam-induced oxidative stress in the nervous system and under normal conditions

	Model indus	Loturi exp.	Durată exp.	Tip de probe	Determinări
Curcumin (CUR) 150 mg/kg/day, oral	oxidative stress induced with diazepam, 2 mg/kg, i.p.	Control CUR + CMC DZP + CMC DZP + CUR + CMC	4 weeks treatment with CUR	brain (frontal, hipocampus)	NF-kβ pNF-kβ ERK ½ iNOS
Allicin (ALI)	Status redox normal	*In vivo* (adm. orală): Control Alicină (ALI): dose 1: 1.25 mg/kg dose 2: 2.5 mg/kg dose 3: 5 mg/kg	2 weeks	whole blood	WBC, LYM, MON, NEU, LYM%, MON%, NEU%, CAT, SOD, GSH, TP, ALB, IgA, IgG, IgM
					molecular docking
		In vitro: Control Alicină (ALI): dose1: 10 µg/mL dose 2: 30 µg/mL dose 3: 60 µg/Ml dose 1 + GSH 1mM dose 2 + GSH 1mM dose 3 + GSH 1mM	24 h	supernatant cells	CAT, SOD, TP, IgA, IgG, IgM
					molecular docking

Caption: DZP - diazepam; CUR - curcumin; CMC - carboxymethylcellulose; NF-kβ - nuclear factor kβ; pNF-kβ - nuclear factor kβ phosphorilated; ERK ½ - extracellular signal-regulated kinase; iNOS - NO sintase inducible; WBC - white blood cells; LYM - limphocytes; MON - monocytes; NEU - neutrophils; LYM/MON/NEU % - limphocytes %, monocytes %, neutrophils %; CAT - catalase; SOD - superoxid dismutase; GSH - glutathione reduced; TP - total proteins; ALB - albumin; IgA/G/M - immunoglobulin A/G/M.

Both compounds of plant origin were tested in vivo on white Wistar rats, male in the case of curcumin and female in the case of allicin, 4 months old, weighing 230 ± 20 g. The experimental groups included 10 animals/group. The researches were carried out in accordance with Directive 2010/63 / EU and with the Agreement of the Ethics Committee of the University of Medicine and Pharmacy "Iuliu Haţieganu" (for the curcumin experiment), respectively of the USAMV Cluj-Napoca (for the allicin experiment). The animals were kept under appropriate zoo hygienic conditions, light / dark rhythm 12h / 12h, with free access to the normal-calorie pellet and water. Sampling was performed following neuroleptanalgesia with a mixture of ketamine - xylazine (90 mg/kg body ketamine + 10 mg/kg body xylazine) (Sevastre-Berghian et al., 2017).

5.3. The modulatory role of the curcumin in antioxidative reaction *via* ERK ½ - NF-kβ in hippocampus and frontal lobe after diazepam treatment

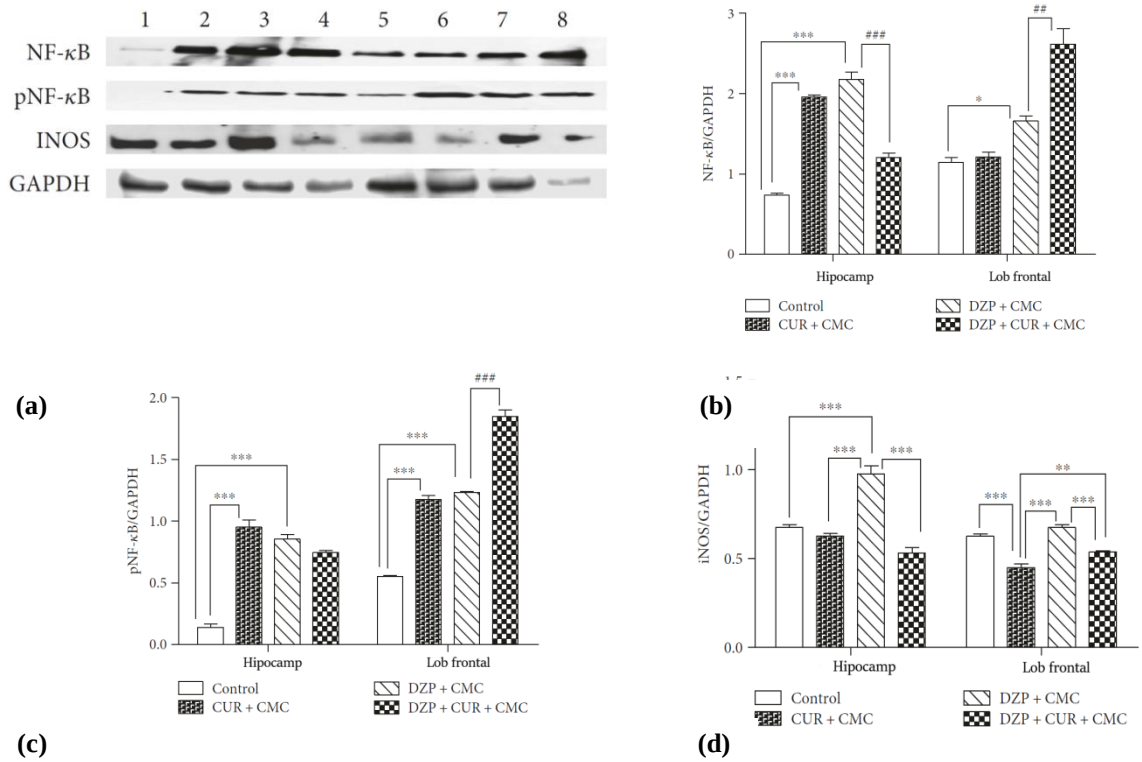

Fig. 9. Effect of curcumin administration on NF-kβ, pNF-kβ and iNOS expression in the hippocampus and frontal lobe. The expression of NF-kβ, pNF-kβ and iNOS was analyzed by Western blot, the bands were measured by densitometry, and the results were normalized to GAPDH. (a) Western blot: 1 - 4 - hippocampus (1: Control, 2: CUR + CMC, 3: DZP + CMC, 4: DZP + CUR + CMC); 5 - 8 - frontal lob (5: Control, 6: CUR + CMC, 7: DZP + CMC, 8: DZP + CUR + CMC). (b) NF-kβ expression; (c): pNF-kβ expression; (d): iNOS expression. * p <0.05 compared to Control / CUR + CMC; ** p < 0.01 relative to Control / CUR + CMC; *** p < 0.001 in relation to Control / CUR + CMC; $^{\#\#}$ p < 0.01 compared to DZP + CMC; $^{\#\#\#}$ p < 0.001 compared to DZP + CMC. Results were expressed as mean ± SEM.

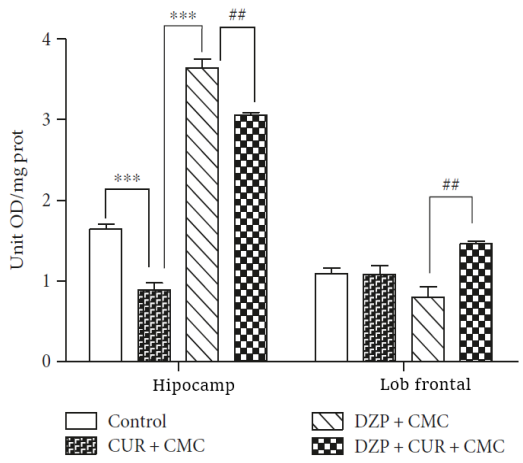

Fig. 10. Effect of curcumin on ERK ½ expression in the brain (hippocampus and frontal lobe). In the hippocampus, ERK ½ level was significantly lower in curcumin-treated animals compared to Control (p < 0.001). Diazepam administration significantly increased ERK ½ expression (p < 0.001) compared with curcumin. In the frontal lobe, co-administration of diazepam and curcumin increased ERK ½ expression (p < 0.01). Results were expressed as mean ± SEM. $^{\#\#}$ p < 0.01 compared to DZP + CMC; *** p < 0.001 in relation to Control / CUR + CMC (Sevastre-Berghian et al., 2017).

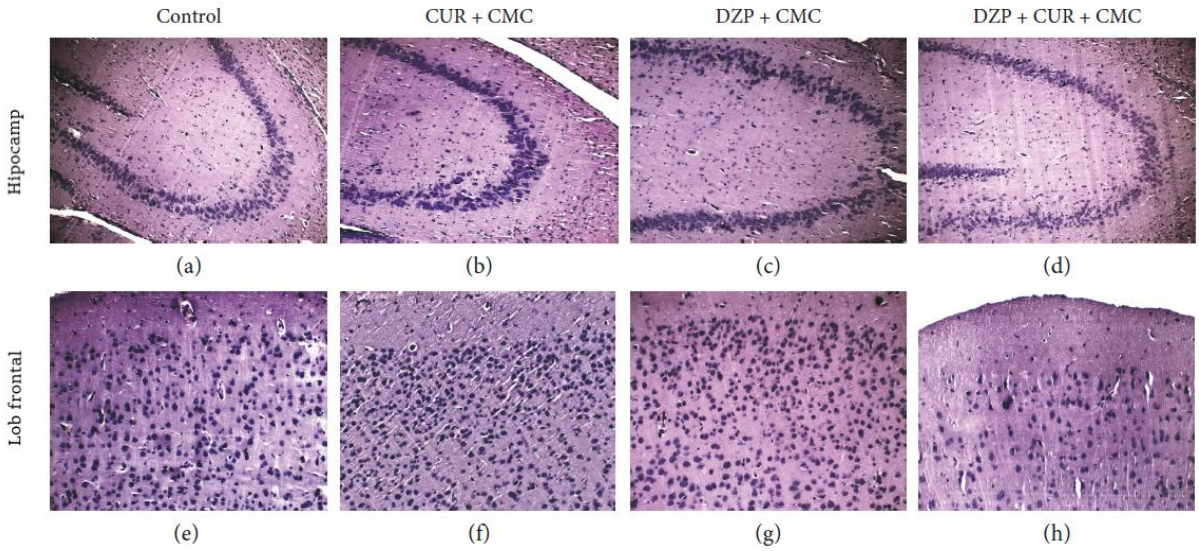

Fig. 11. Histological appearance of the hippocampus (a, b, c, d) and the frontal lobe (e, f, g, h), in the Control group and in the experimental groups, following treatment with curcumin and diazepam. The administered treatment did not induce detectable structural changes in the hippocampal CA3 area (a-d) or in the prefrontal cortex (e-h). x 200, col. HE (Sevastre-Berghian et al., 2017).

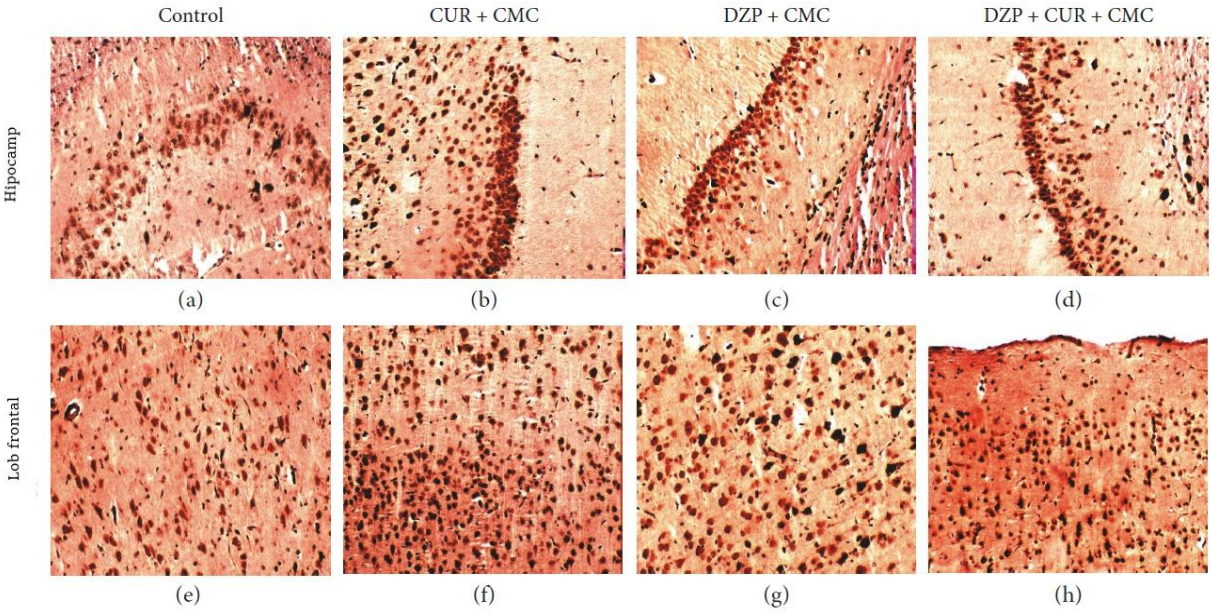

Fig. 12. Immunohistochemical evaluation of iNOS expression in the hippocampus (a-d) and in the prefrontal cortex (e-h), in the Control group and experimental groups. Immunocolouring showed a decrease in iNOS expression in CA3 area and prefrontal cortex, in the DZP + CUR + CMC group, compared with the DZP group. x 200 (Sevastre-Berghian et al., 2017).

5.4. Allicin modulatory effect on the oxidative stress and immune reaction

5.4.1. Oxidative stress and humoral immune reaction after allicin treatment

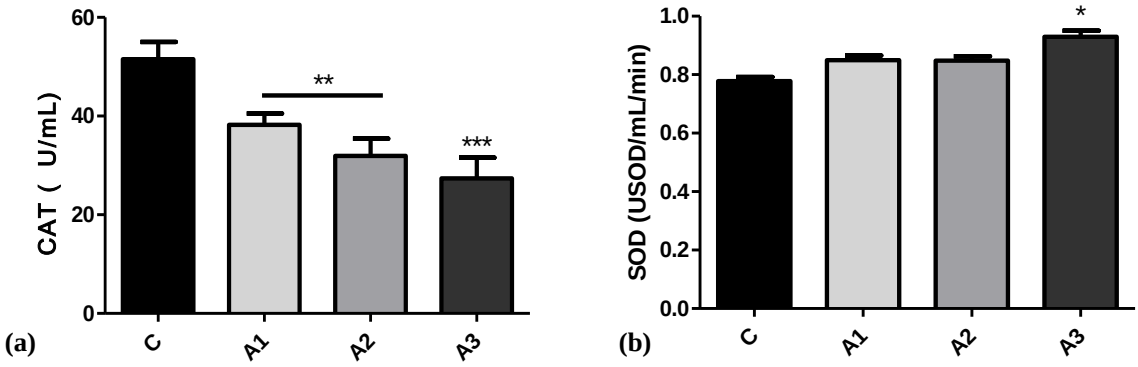

Fig. 13. The activity of CAT (a) and SOD (b) in the Control and experimental groups. Allicin significantly decreases CAT activity, while SOD activity did increase or statistically significantly increase (at the dose of 60 mg/kg allicin body). Values are expressed as mean ± SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Toma et al., 2019).

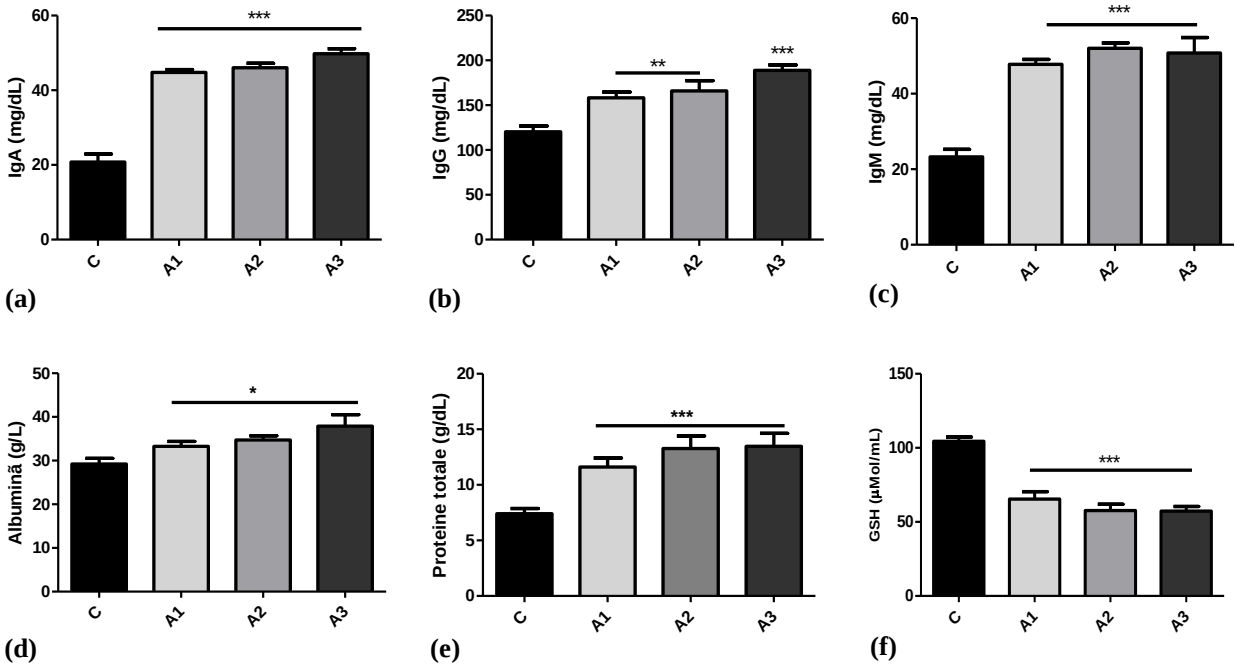

Fig. 14. Serum concentrations of IgA (a), IgG (b), IgM (c), albumin (d), total protein (s) and GSH in the Control and allicin treated animals. Allicin treatment induced the prominent increase of immunoglobulins relative to the Control, as well as the increase of the total serum protein concentration. Albumin showed a slight increase ($p < 0.05$), and GSH showed a marked decrease ($p < 0.001$). Results were expressed as mean ± SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Toma et al., 2019).

Tabel 16. The values of the main leukocyte indicators in the hemogram. Allicin treatment did not cause statistically significant changes. Values are expressed as mean ± SD. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

	C	ALI 1.25 mg/kg	ALI 2.5 mg/kg	ALI 5 mg/kg
WBC (10^9/L)	14.5 ± 1.63	13.1 ±1.23	13.4 ± 1.02	14.2 ± 2.14
LYM (10^9/L)	10.1 ± 1.49	9.7 ± 1.24	10.5 ± 1.02	11.0 ± 1.76
MON (10^9/L)	0.3 ± 0.10	0.2 ± 0.08	0.3 ± 0.31	0.2 ± 0.09
NEU (10^9/L)	2.8 ± 0.13	3.2 ± 0.12	2.7 ± 0.20	2.9 ± 0.45
LYM%	76.4 ± 1.93	73.5 ± 2.80	75.1 ± 2.78	77.8 ± 2.20
MON%	2.08 ± 0.85	1.57 ± 0.97	2.2 ± 2.04	1.30 ± 0.47
NEU%	20.8 ±1.26	25.1 ± 1.73	21.7 ± 3.35	20.9 ± 2.06

Caption: WBC - white blood cells; LYM - limphocytes; MON - monocytes; NEU - neutrophils; LYM/MON/NEU % - % of limphocytes, monocytes, neutrophils

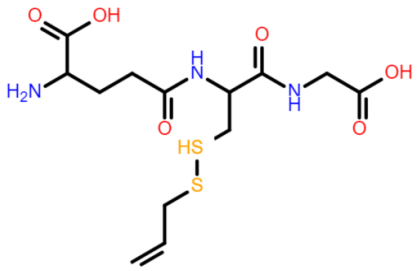

Fig. 15. Structure of S-allyl mercaptoglutathione, constructed in Gauss View Version 5 (after Dennington et al., 2018).

Tabel 17. Energy and geometric interaction characteristics of scavenger receptors in interaction with SAMG

Ligand	Tip	Energie de legare (kcal/mol)	Specificitate geometrică
Colec12	SCAR A	−6.7	Foarte mare
MARCO	SCAR A	−5.7	Foarte mare
Msr1	SCAR A	−4.7	Foarte scăzută
SCARA 3	SCAR A	−4.8	Foarte scăzută
SCARA 5	SCAR A	−5.0	Scăzută
SCARB 1	SCAR B	−5.7	Foarte mare

Caption: Colec12 - scavenger receptor with lectin C domain; MARCO - macrophage receptor with collagen structure; Msr1 - macrophage scavenger receptor 1; SCARA 3/5 - scavenger receptors class A type 3 and 5; SCARB 1 - scavenger receptors class B type 1

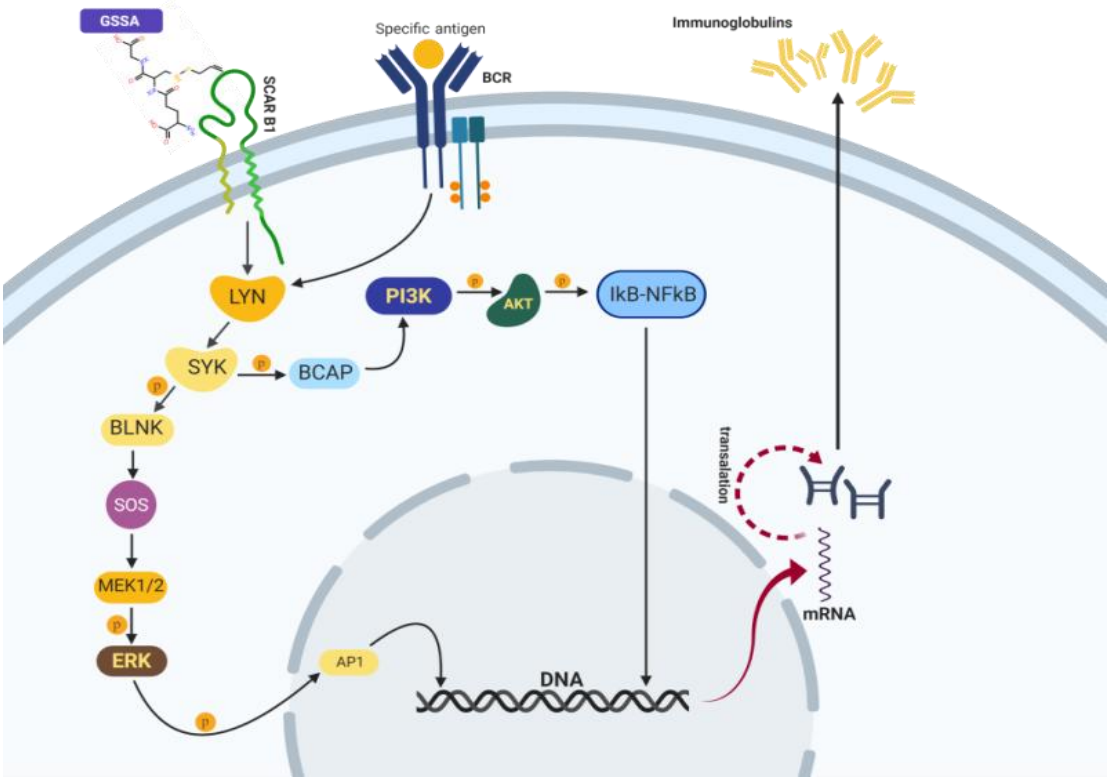

Fig. 20. The synthesis pathway of immunoglobulins, by CD19 + lymphocyte B, under the action of SAMG.

6. *IN VIVO* ACTION OF THE SEVERAL VEGETAL EXTRACTS IN SOME PATHOLOGIES ASSOCIATED WITH REDOX IMBALANCES

6.1. Experimental design

Tabel 18. Experimental design of in vivo testing of plant extracts, in order to establish the specific bioactivity. MHA - alcohol matrix; MHGA - hydroglycerol matrix; MCMC - carboxymethylcellulose matrix.

Extract	Pathology	Experimental groups	Experiment period	Samples	Analyses
Lamium album (LA), *Lamium purpureum* (LP) - MHA -	restraint stress	**Control** **Stress** (2h/day) **Extract LA** (200 mg/kg/day) **Extract LP** (200 mg/kg/day) **Stress + Extract LA** **Stress + Extract LP**	17 days	blood	CHOL, TGL, AA, , CAT, TBARS, CS
				liver, kidney, adrenals, thymus	HE
				brain	Col. HE, CHOL, CS, CAT, AA, TBARS, TNFα,
Vaccinium vitis-idaea - MHA -	liver and kindey ethanol toxicosis	**Control** **Extract** (200 mg/kg/day) (**E**) **Alcool** (6 g/kg ethanol 50%/day) **Extract + Alcool**	15 days	blood	UREA, CREA, TGO, TGP, CHOL, GLUC
				liver, kidney	HE

Galium verum - MHA -	restraint stress	**Control** **Extract** (250 mg/kg/day) **Stress** (3h/day) **Extract + Stress**	15 days	hypothalamus, pituitary gl., adrenals	Nissl, HE, Hurduc
Malus sylvestris - MHGA -	steatohepatitis induced with CCl_4	**Control** **Extract** (200 mg/kg corp/zi) **CCl_4** (700 µL/kg corp/zi) **CCl_4 + Extract**	7 days	blood	ALT, AST, WBC, LYM, TNFα
				liver	HE
Hypericum perforatum și H. maculatum - MCMC -	anxiety induced by FG-7142	**Control** (CMC) **FG-7142** (7.5 mg/kg corp, i,p. doză unică) **APZ + FG-7142** (APZ, 0.08 mg/kg corp) **Q + FG-7142** (Q, 30 mg/kg corp) **HM + FG** (HM, 350 mg/kg corp) **HP + FG** (HP, 350 mg/kg corp)	22 days	blood	CS
				brain	MDA, CAT, SOD, IL-1α, IL-1β, MCP1, IFN, MIP, RANTES, NF-kβ, pNF-kβ
Cornus mas (CM) - MHA -	apoptosis induced with silver nanoparticles (AgNP)	**Control** **T7D1** AgNP-CM **T7D2** Ag-NP-CM **T15D1** Ag-NP-CM **T15D2** Ag-NP-CM	15 days	testis	HE TUNEL

Caption: CHOL - cholesterol; TGO / AST - oxaloacetic glutamate transaminase; TGP / ALT - pyruvic glutamate transaminase; UREA - urea; CREA - creatinine; CAT - catalase; TBARS - reactive species with thiobarbituric acid; CS - corticosterone; AA - adrenaline; GLUC - glucose; WBC - leukocytes; LYM - lymphocytes; TNFα-Tumor Necrosis Factor α; MDA - malondialdehyde; SOD - superoxide dismutase; IL-1α / 1β - interleukin 1α / 1β; MCP1-macrophage chemoattractant protein1; IFN - interferon; MIP - macrophage inflammatory protein 1; RANTES - factor regulating secretory function and T lymphocyte adhesion; NF-kβ / pNF-kβ - nuclear factor kβ / activated form.

6.3. Chemical composition and the action of the *Lamium album* L. and *Lamium purpureum* L. extracts on several blood and histological parameters after restraint stress exposure

Tabelul 19. Content of chlorogenic acid, rosmarinic acid, rutoside, caffeic acid and iridoid subtypes (SME, ASME) in ethanol extract of *L. album* and *L. purpureum.* Results are expressed as mean ± SD.

Specia	mg/100g dry material					
	Chlorogenic acid	Rosmarinic acid	Rutoside	Caffeic acid	SME[27]	ASME[28]
Lamium album	119.2 ± 1.8	98.0 ± 1.95	290.7 ± 2.30	795.4 ± 1.43	18.7 ± 1.54	22.6 ± 1.64
Lamium purpureum	23.03 ± 0.06	105.21 ± 2.01	21.97 ± 0.66	83 ± 1.74	-	-

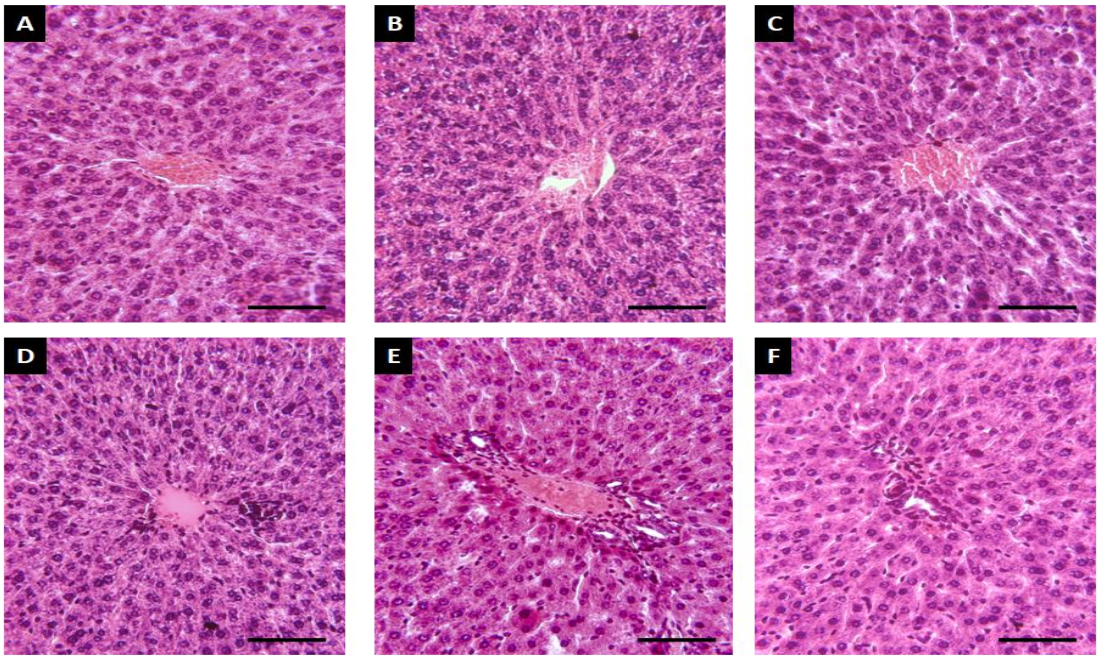

Fig. 21. Microscopic appearance of the liver in Control (A), Stress - S (B), *L. album* - LA (C), *L. purpureum* - LP (D), Stress + LA - SLA (E) and Stress + LP - SLP (F). H&E, x 400, scale = 25 µm.

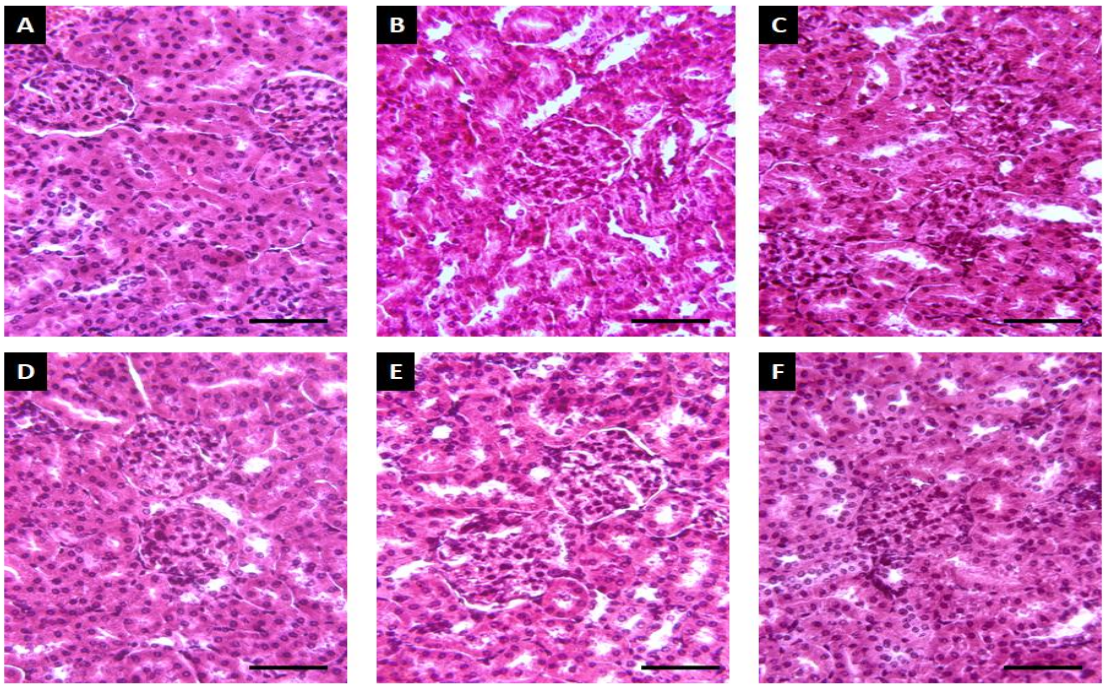

Fig. 22. Histopathological appearance of the kidney in Control (A) and experimental groups. Stress - S (B), *L. album* - LA (C), *L. purpureum* - LP (D), Stress + LA - SLA (E) and Stress + LP - SLP (F). H&E, x 400, scale = 25 µm.

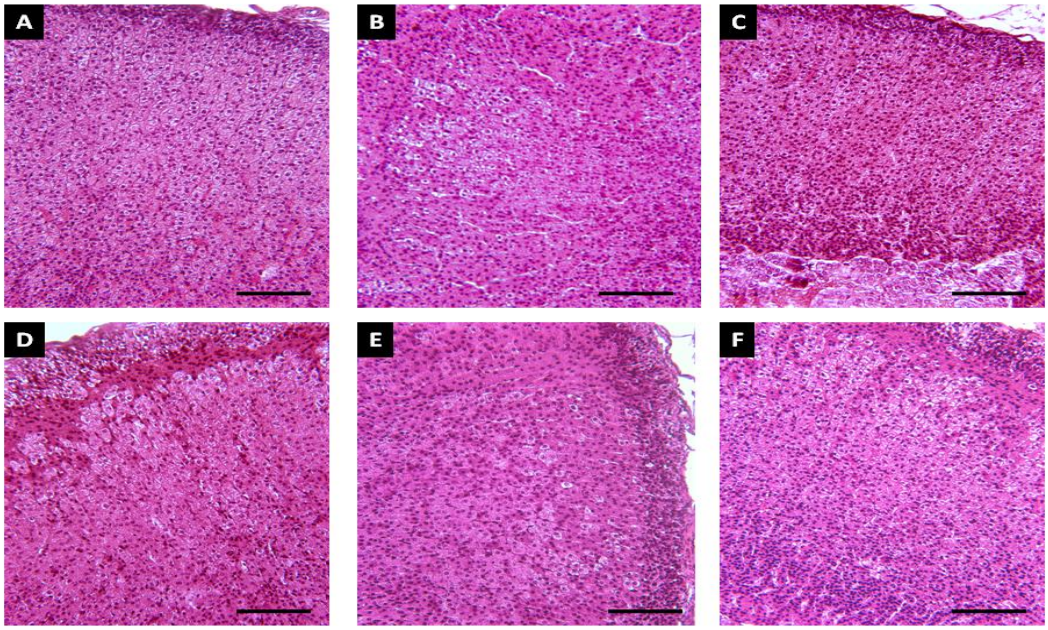

Fig. 23. Structure of the adrenal gland in the Control and experimental groups exposed to stress and/or treatment with extracts of *L. album*, respectively *L. purpureum*. Control (A), Stress - S (B), L. album - LA (C), L. purpureum - LP (D), Stress + LA - SLA (E) and Stress + LP - SLP (F). H&E, x 200, scale = 50 μm.

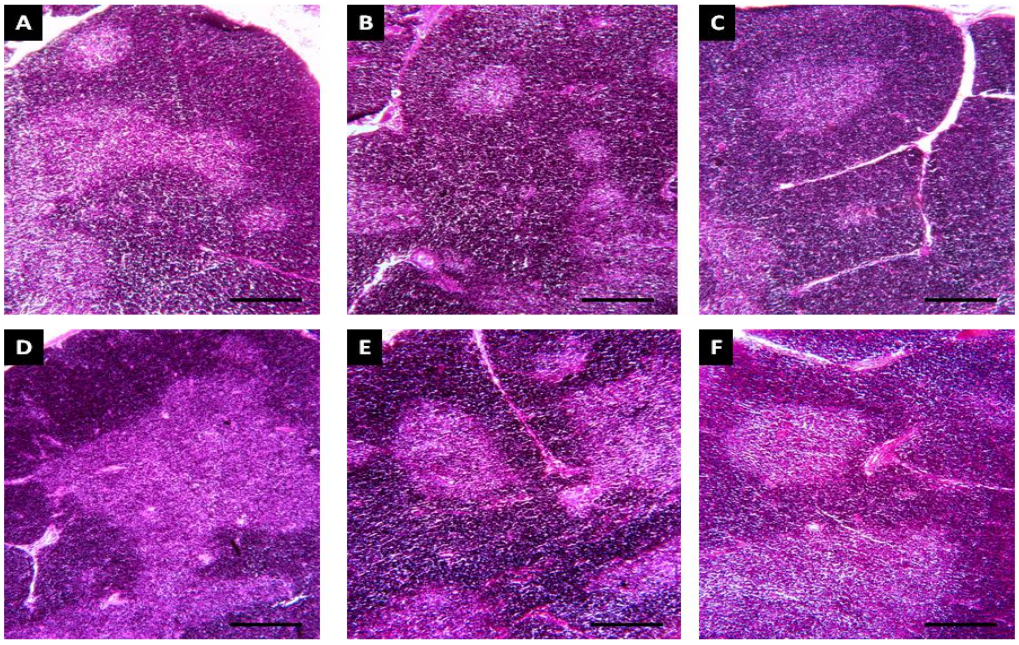

Fig. 24. Microscopic structure of the thymus in Control and experimental groups. Control (A), Stress - S (B), *L. album* - LA (C), *L. purpureum* - LP (D), Stress + LA - SLA (E) and Stress + LP - SLP (F). H&E, x 200, scale = 50 μm.

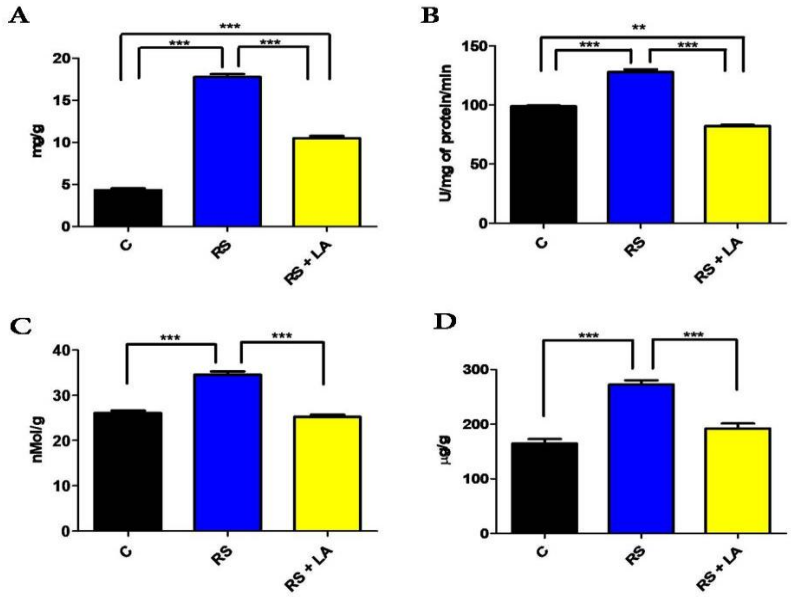

Fig. 25. Cholesterol (A), CAT (B), TBARS (C) and CS (D) values in the cerebral lysate (hippocampus) in the Control and experimental groups. Values are expressed as mean ± SD. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

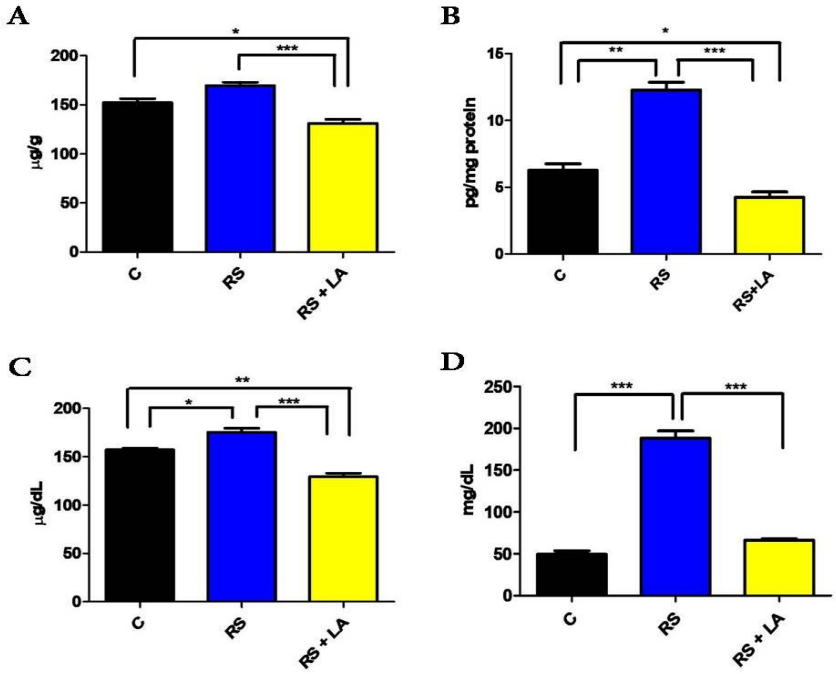

Fig. 26. The values of adrenaline (A) and TNFα (B) concentration in the hippocampus and blood concentration of corticosterone (C) and cholesterol (D) in Control and experimental groups. Values are expressed as mean ± SD. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

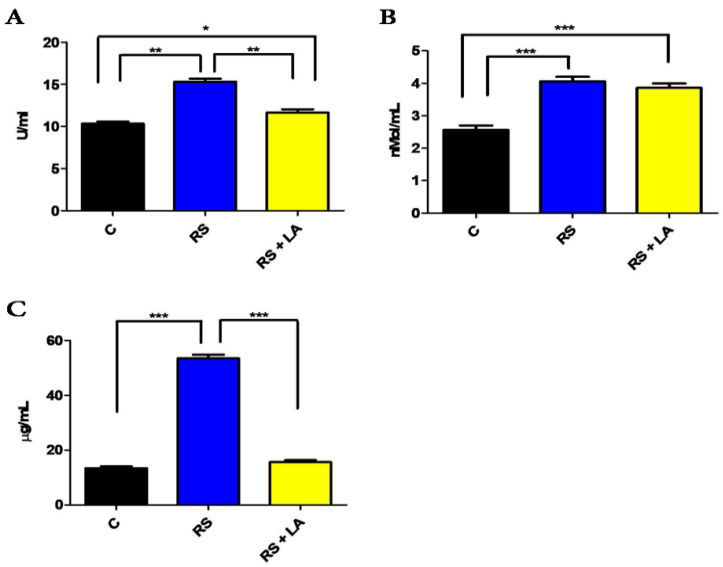

Fig. 27. The blood values of CAT activity (A), TBARS concentration (B) and AA (C) in the Control and experimental groups. Values are expressed as mean ± SD. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

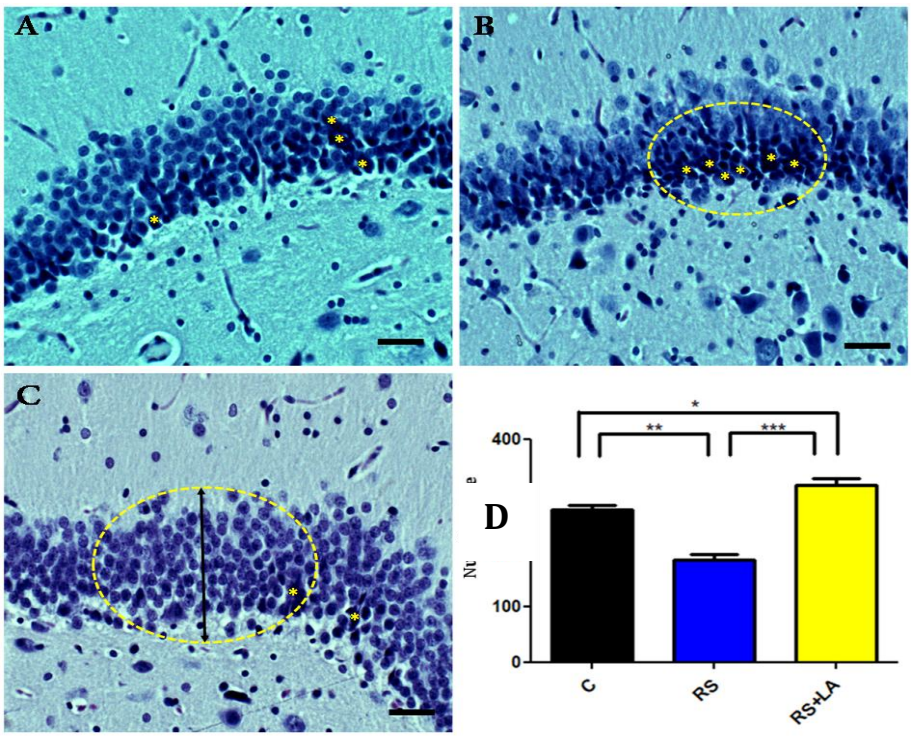

Fig. 28. The structure of the dentate gyrus in Control and experimental groups. In relation to Control (A), in animals exposed to repeated restraint stress - group RS (B), dark neurons (marked with a yellow asterisk) were identified, in the subgranular area, with the tendency to expand in the granular territory and to thin the cell cord (dotted line). The administration of *L. album* extract - RS + LA group (C), determined the regeneration of the dentate gyrus, marked by the absence of dark neurons and by the expansion and growth of the number of granular cell layers of the dentate gyrus. The regenerative process induced by *L. album* was also verified by counting all the cells in the dentate gyrus (D), after which the significant variation between the experimental groups could be observed, regarding the number of cells present in the dentate gyrus. HE, x400, scale = 10 µm.

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6.4. Chemical composition and the protective action of the *Vaccinium vitis-idaea* L. extract on liver and kidney after chronic exposure of the Wistar rat to ethanol

Tabelul 21. The values of blood biochemical parameters in Control and experimental groups. C -Control; E - Extract from *V. vitis-idaea*; A - ethyl alcohol; AE - Ethyl alcohol + Extract from *V. vitis-idaea*. Values are expressed as mean (m) ± SD. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

	C	E	A	AE
GLUC (mg/dL)				
m ± SD	140.33 ± 5.17	143.66 ± 4.13	138.66 ± 9.04	129.66 ± 3.86
CHOL (mg %)				
m ± SD	111.17 ± 5.92	99.82 ± 8.02	89.34 ± 6.85*	104.20 ± 6.65
GOT (µg pyr/mL)				
m ± SD	745.56 ± 46.47	750.93 ± 19.44	739.63 ± 31.06	747.67 ± 11.53
GPT (µg pyr/mL)				
m ± SD	216.9 ± 25.18	197.98 ± 17.79	341.1 ± 48.83*	396.9 ± 33.4***
UREA (mg/dL)				
m ± SD	51.35 ± 2.35	51.72 ± 2.49	40.61 ± 0.59**	40.57 ± 1.15**
CREA (mg/dL)				
m ± SD	0.39 ± 0.064	0.37 ± 0.056	0.54 ± 0.06*	0.47 ± 0.056*

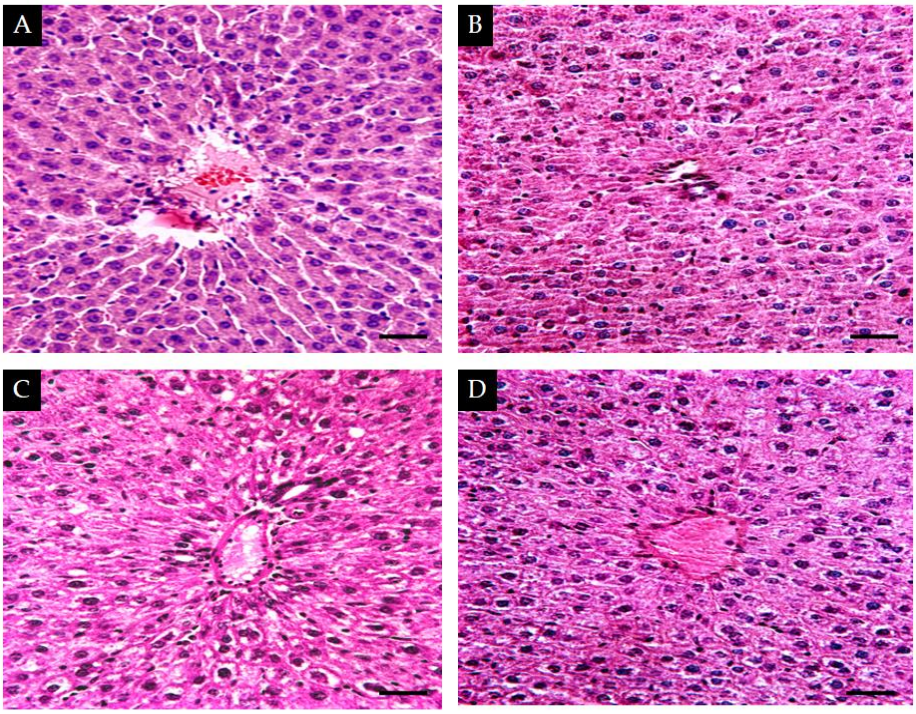

Fig. 29. Histological appearance of the liver in the Control group (A), Extract (B), Alcohol (C) and Alcohol + Extract (D). HE, x400, scale = 25 µm.

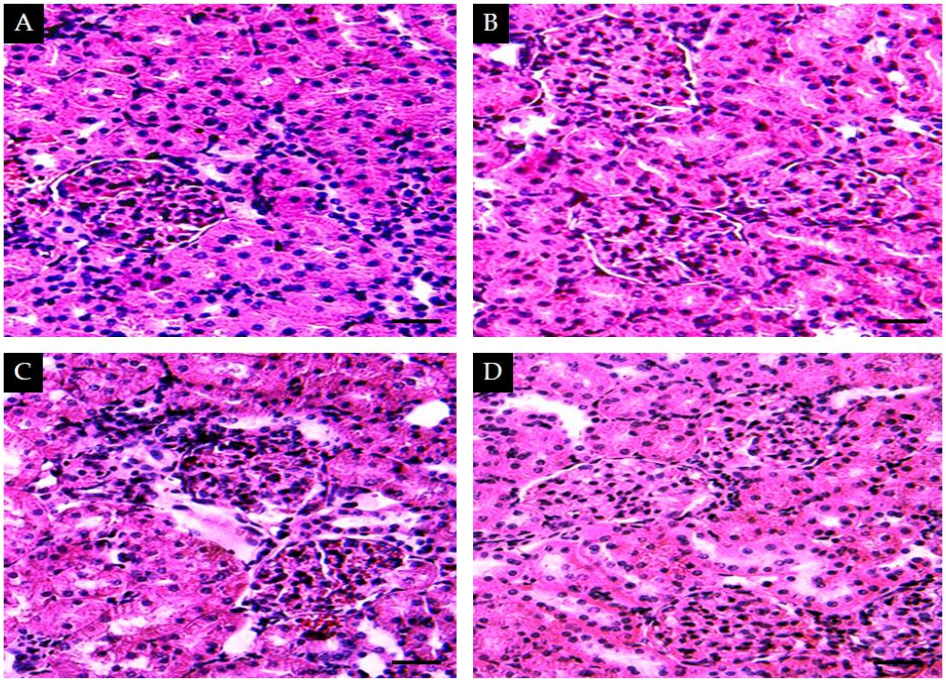

Fig. 30. Histological appearance of the kidney in Control (A), Extract (B), Alcohol (C) and Alcohol + Extract (D). Col. HE, x400, scale = 25 μm.

6.5. The action of the *Galium verum* L. extract on the hypothalamus - pituitary - adrenals axis in the restraint stress conditions

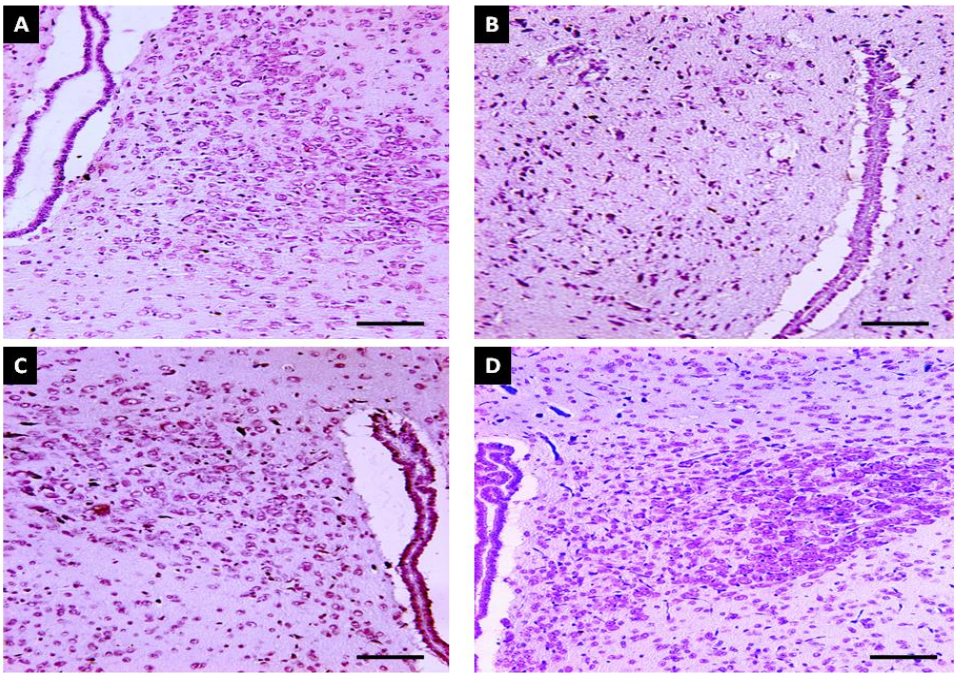

Fig. 31. The neurosecretory activity of the paraventricular nucleus in Control (A), Stress (B), in the group treated with *G. verum* extract (B) and in the animals exposed to stress and treated with *G. verum* extract (D). Nissl, x200, scale = 50 μm.

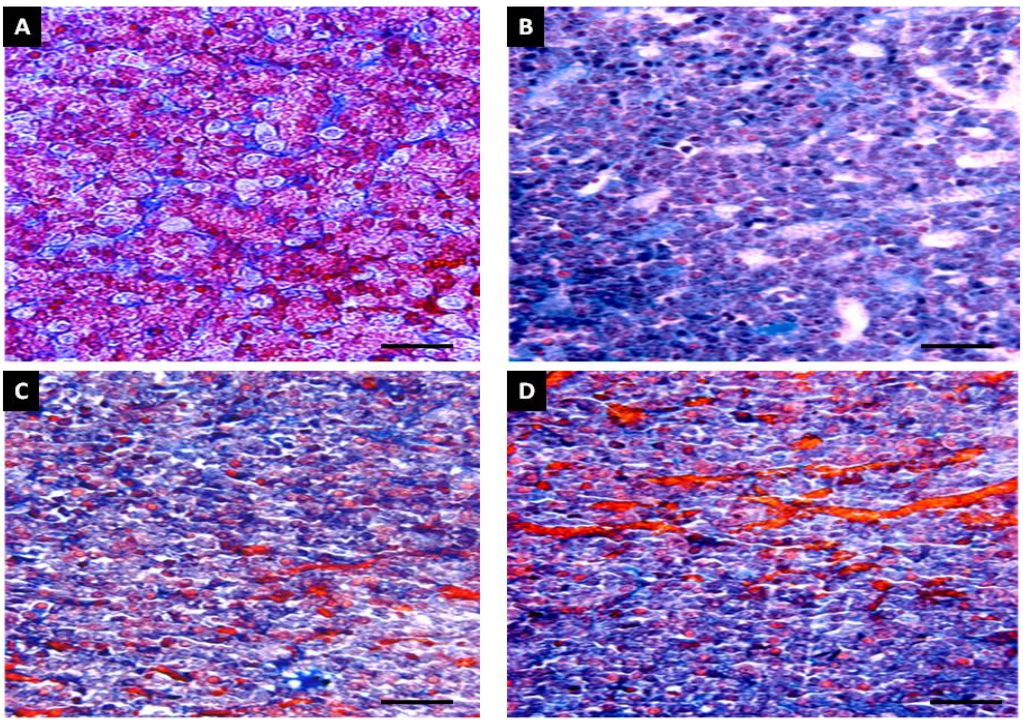

Fig. 32. Structure of adenohypophysis in Control (A) and experimental groups: Stress (B), treatment with *G. verum* (C) and in animals exposed to stress and treated with *G. verum* extract (D). Hurduc, x400, scale = 25 μm.

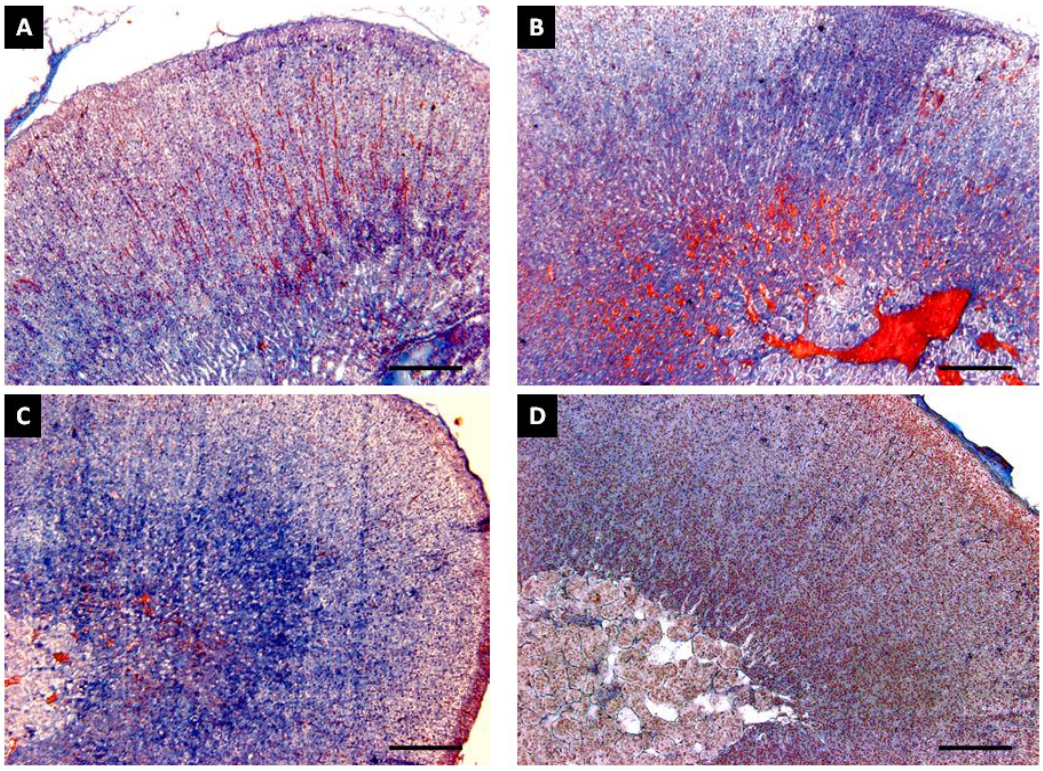

Fig. 33. Structure of the adrenal gland in Control (A) and experimental groups: Stress (B), treatment with *G. verum* (C) and individuals exposed to stress and treated with *G. verum* extract (D). HE, x100, scale = 100 μm.

6.6. The effect of the *Malus sylvestris* Mill. extract on the steatotic liver. Correlations with the inflammatory reaction

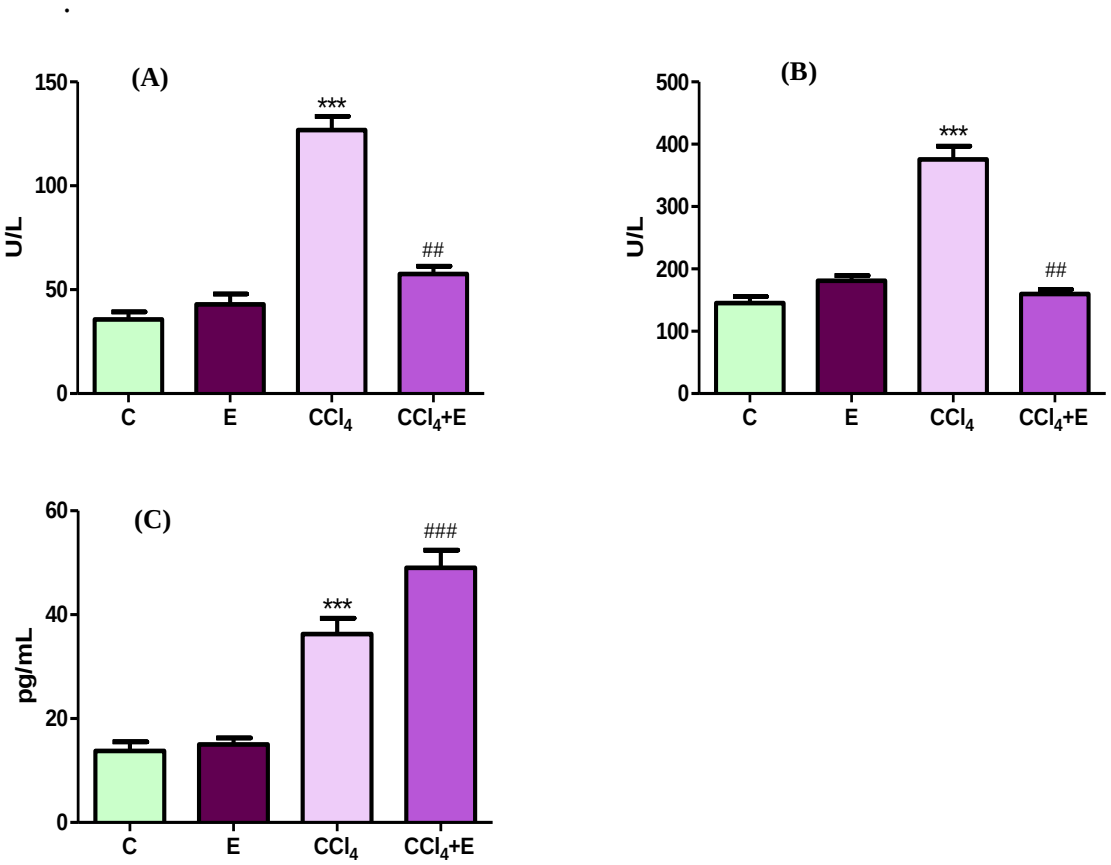

Fig. 34. The values of ALT (A), AST (B) and TNFα (C), in Control and experimental groups, following administration of CCl_4 respectively of the extract of *M. sylvestris* + CCl_4. Values are expressed as mean ± SD.* $p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

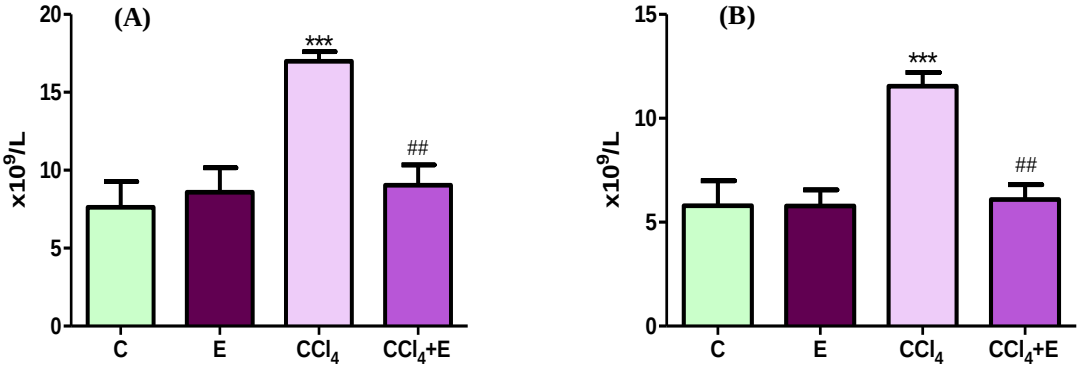

Fig. 35. The number of total leukocytes (A) and lymphocytes (B) in Control and experimental groups. Values are expressed as mean ± SD.* $^{/\#}p < 0.05$; $^{**/\#\#}p < 0.01$; *** $^{/\#\#\#}p < 0.001$. * - comparison with Control; # - comparison with CCl_4.

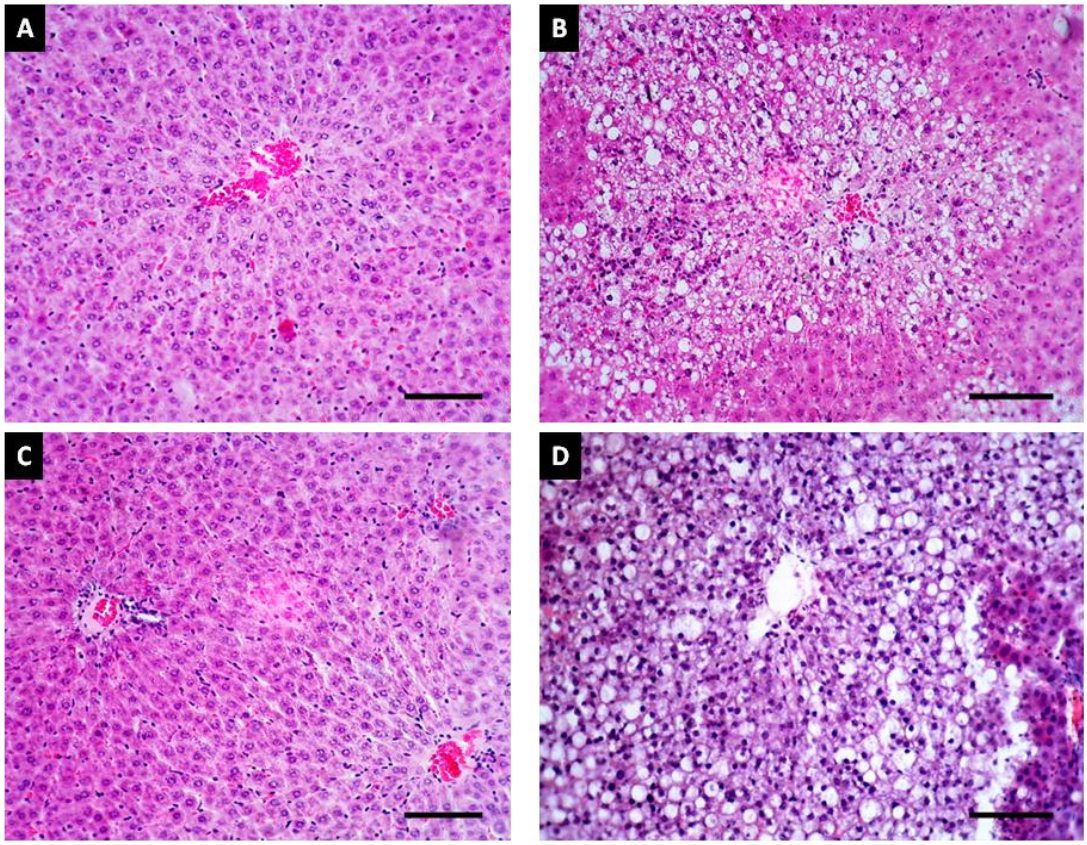

Fig. 36. The microscopic structure of the liver in Control and experimental groups. Control - (A); CCl_4 - (B); Extract of *M. sylvestris* - (C); Extract of *M. sylvestris* + CCl_4 - (D). HE, x400, scale = 20 μm.

6.7. The action of the *Hypericum perforatum* L. and *Hypericum maculatum* Crantz extracts in Wistar rat with anxious disorder

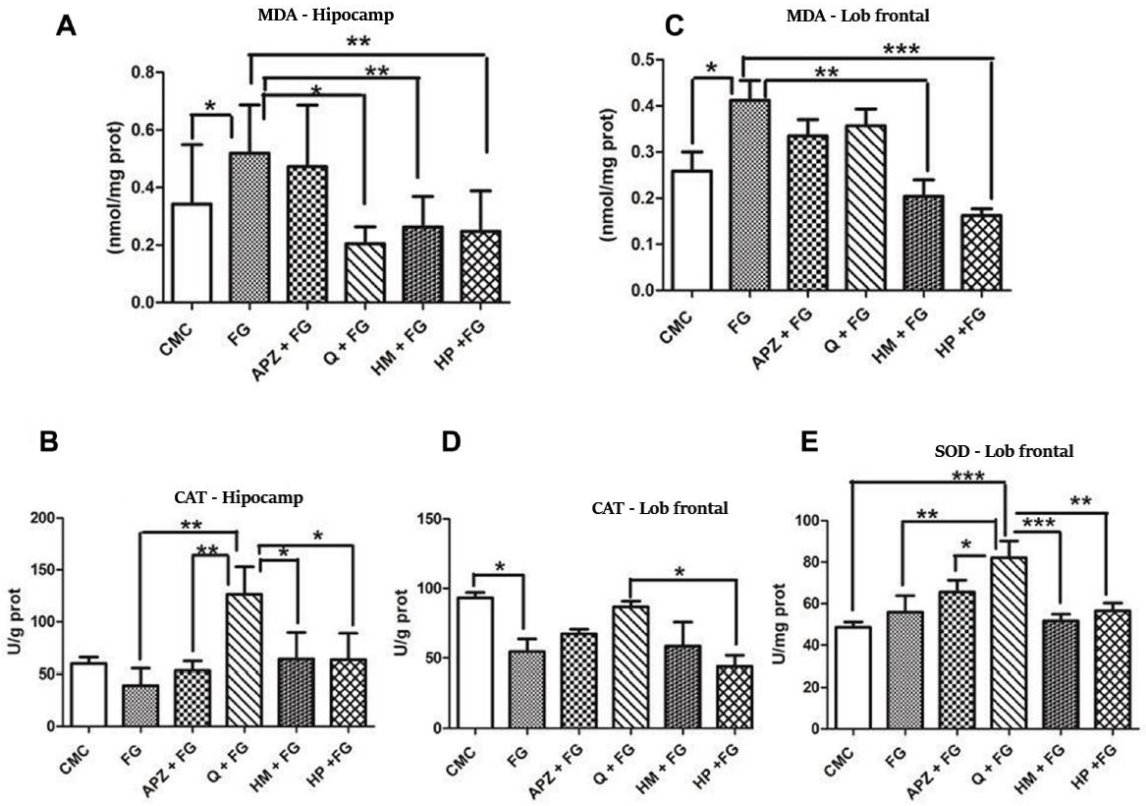

Fig. 37. The action of natural compounds and Hypericum extracts on the redox balance in the hippocampus and frontal lobe. Quercetin, H. maculatum (HM) and H. perforatum (HP) decreased the level of MDA in the hippocampus (A); HM and HP decreased lipid peroxidation in the frontal lobe (C). The MDA showed a high concentration in the hippocampus and frontal lobe in the FG group (A, C). In the hippocampus, CAT was low after FG administration, but the differences were not significant compared to the CMC group. After 21 days of Q treatment, CAT was increased (B, D) in both the hippocampus and frontal lobe. Q decreased SOD activity in the frontal lobe (no changes were observed in the hippocampus so we did not present the values). Values are expressed as mean ± SD. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

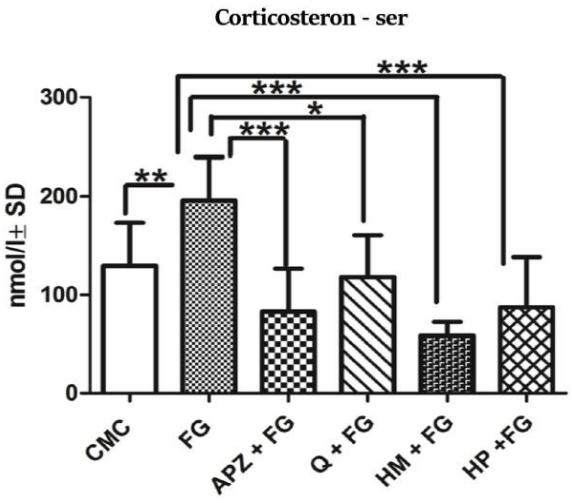

Fig. 38. Serum corticosterone values in Control and experimental groups. Anxiogenic treatment with FG significantly increased serum corticosterone levels, compared with the CMC group; APZ, HM, and HP decreased serum corticosterone. Values are expressed as mean ± SD.* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

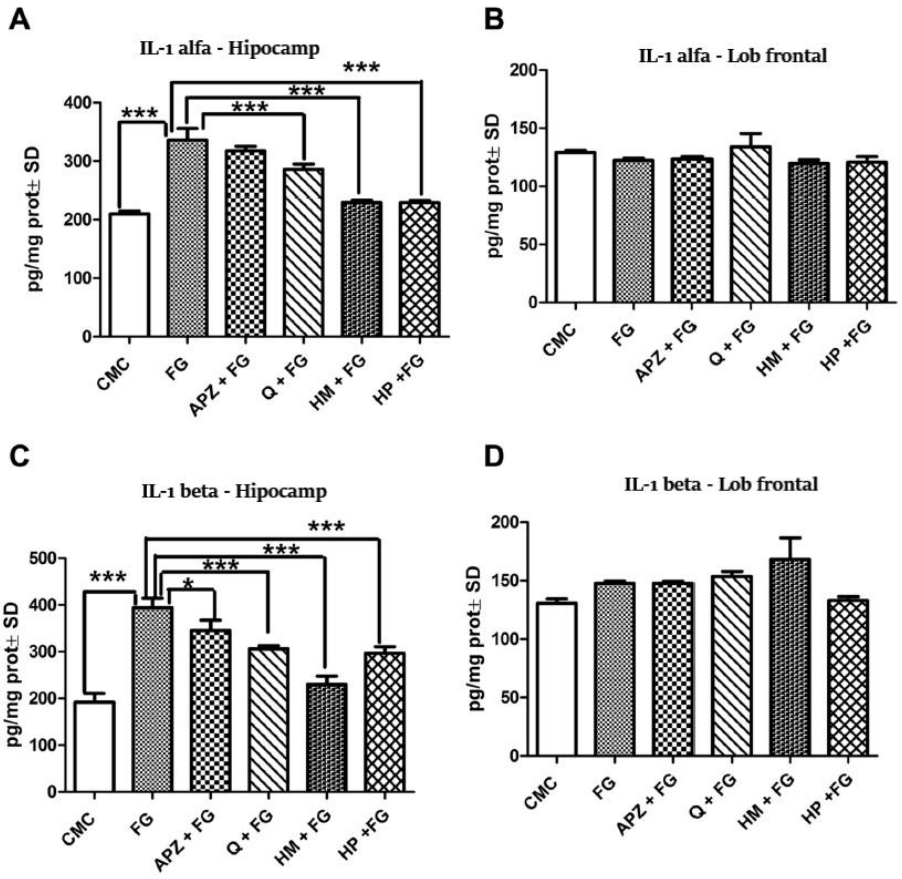

Fig. 39. IL-1α and IL-1β values in the Control and experimental groups. The hippocampus showed significant increases of IL-1α and IL-1β in animals exposed to the anxiety-inducing agent (FG), compared to the CMC group. Q, HM, and HP decreased IL-1α and IL-1β expression in the hippocampus compared to the FG group. APZ administration was associated with decreased IL-1β only in the hippocampus (A, C). Values are expressed as mean ± SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

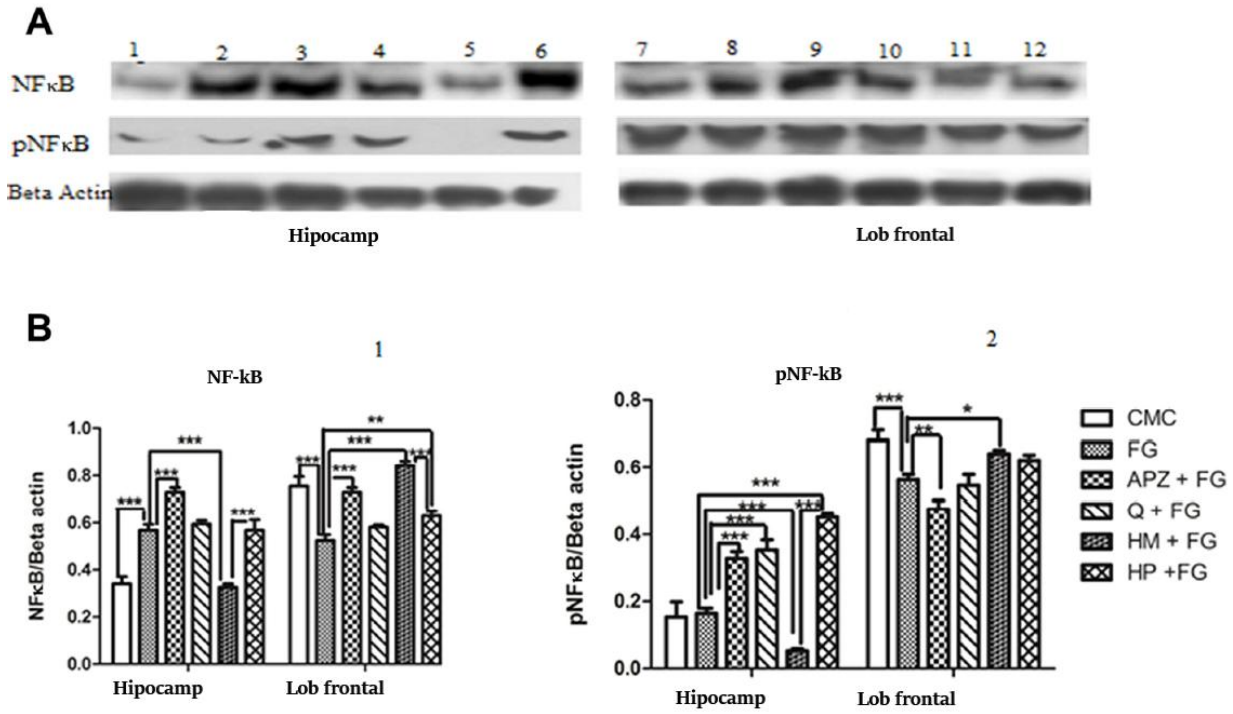

Fig. 42. Quantification of NF-kβ and pNF-kβ expression in the Control and experimental groups. The expression of NF-kβ and pNF-kβ was analyzed by Western blot. The analysis of the images with the bands resulting from the Western blot was performed by densitometry. The results were normalized to β-actin. 1 - 6: hippocampus (1 - CMC; 2 - FG; 3 - APZ FG; 4 - Q FG; 5 - HM FG; 6 - HP FG); 7 - 12: frontal lobe (7 - CMC; 8 - FG; 9 - APZ FG; 10 - Q FG; 11 - HM FG; 12 - HP FG). FG administration significantly increased the level of NF-kβ in the hippocampus and decreased the expression of nuclear factor kβ and its activated form (pNF-kβ) in the frontal lobe compared with the Control group. APZ increased NF-kβ expression in both the hippocampus and frontal lobe. Q stimulated pNF-kβ expression in the hippocampus, whereas, in the frontal lobe, HM administration led to a significant increase of NF-kβ and pNF-kβ. In the hippocampus, HM decreased NF-kβ and pNF-kβ expression. Values are expressed as mean ± SD. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ (Sevastre-Berghian et al., 2018).

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6.8. The effect of the *Cornus mas* L. extract on the arhitecture and apoptosis of the testis

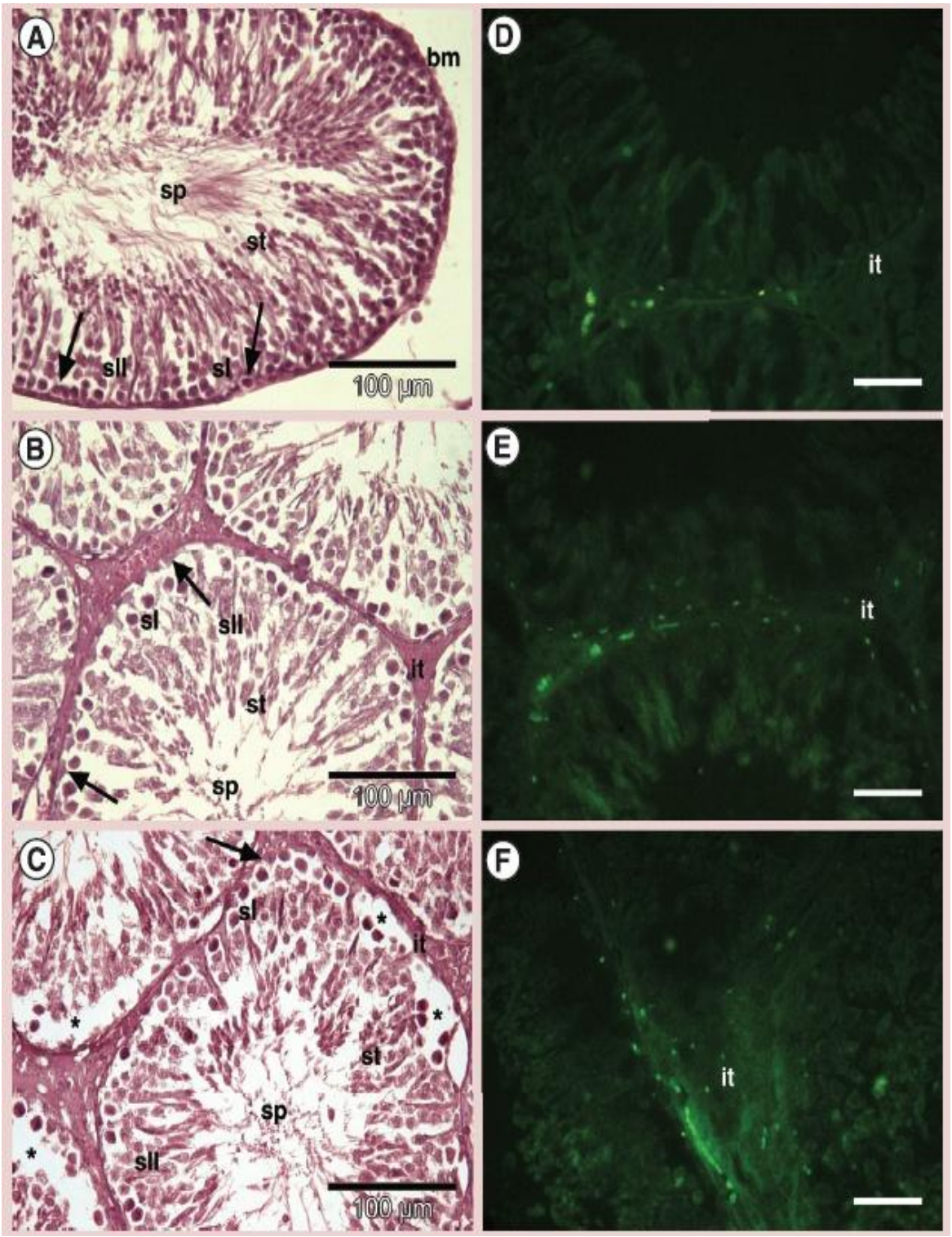


Fig. 43. Aspects of the testicular structure highlighted by HE staining (A - C) (x 100, scale = 100 µm) and evaluation of apoptotic cells by TUNEL (D - F) test (x 400, scale = 20 µm) 7 days after nanoparticles treatment of Ag functionalized with *C. mas*, in the Control group (A, D) and in the experimental groups (B, C, E, F). sl - primary spermatocytes; sll - secondary spermatocytes; st - spermatids; sp - sperm cells. The positive TUNEL signal (green spots) was observed in the interstitial tissue (it) in Control (D), T7D1 (E) and T7D2 (F) (Opriș et al., 2019).

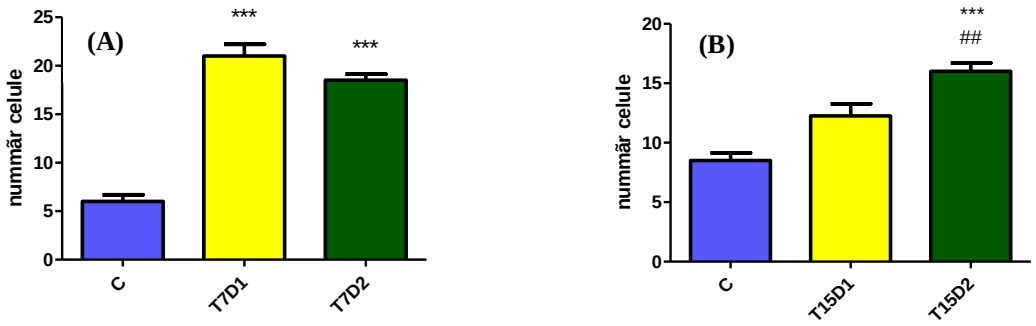


Fig. 45. The number of apoptotic cells at T7 (A) and T15 (B), in Control and experimental groups. Apoptosis was significantly increased in the groups treated with AgNP-CM, compared to the control group, both at 7 and 15 days after cessation of the administration of AgNP-CM. Values are represented as mean ± SD (*** $p < 0.001$, comparison with lot C - Control; $^{\#\#}$ $p < 0.01$, comparison with D2 group).

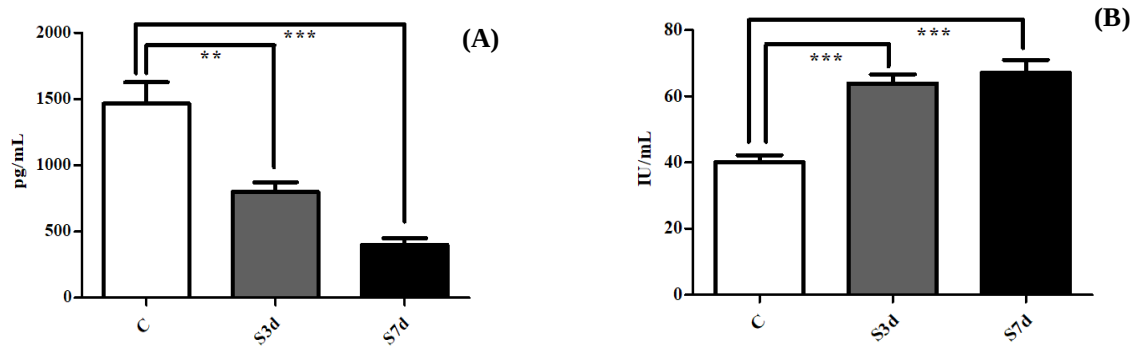
7. OXIDATIVE STRESS INDUCED BY NEUROPSYCHOLOGICAL STRESS - THE BIOLOGY OF THE CELLULAR MECHANISMS FROM HIPPOCAMPUS INVOLVED IN COPING REACTIONS TO STRESSOR

7.1. Experimental design

Tabel 22. The experimental design of the studies regarding the biology of neuropsychological stress and its relation with the redox status

	Probe recoltate	**Analize efectuate**
C - Control	blood	3-NT, CAT, GPX, CS
S3D - 3h/day of restraint stress exposure, 3 consecutive days	brain	Nissl, Acridinorange, CyOx, ATPase, MAO
S7D - 3h/day of restraint stress exposure, 7 consecutive days		

Caption: 3-NT - 3-nitrotyrosine; CAT - catalase; GPX - glutathione peroxidase; CS - corticosterone; CyOx - cytochrome oxidase; ATPase - adenosine tryphophatase; MAO - monoamine oxidase (Toma și colab., 2017).



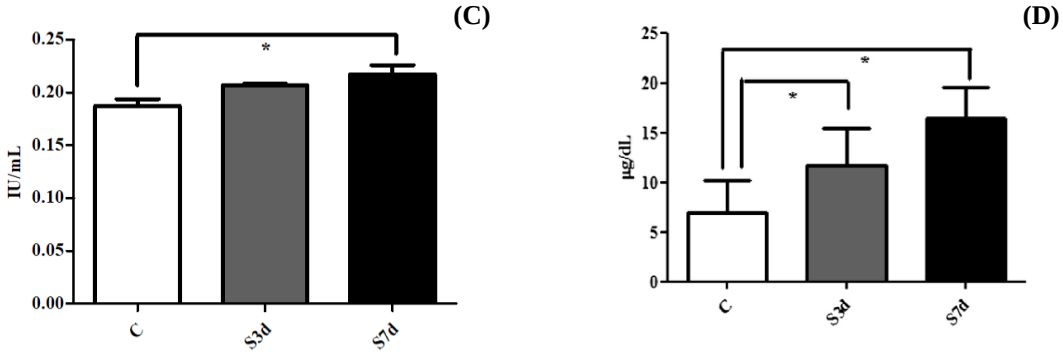
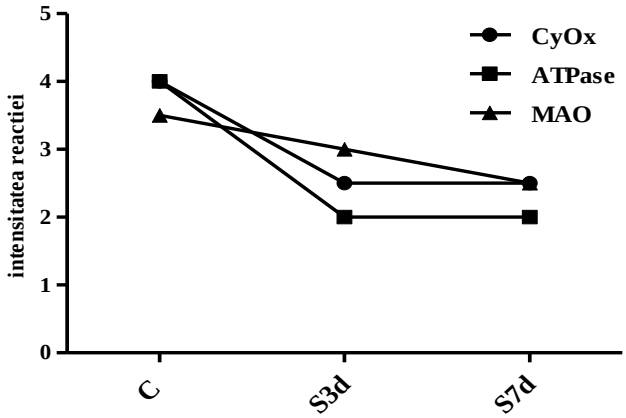


Fig. 46. The 3-NT (A), CAT (B), GPX (C) and CS (D) values in the Control group and in the experimental groups exposed to immobilization stress, for 3 days and 7 days respectively. Values are expressed as mean ± SEM. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (Toma și colab., 2017).



	CyOx	ATPase	MAO
C	4	4	3.5
S3d	2.5	2	3
S7d	2.5	2	2.5

Fig. 47. Determination of CyOx, ATPase and MAO dynamics in Control and experimental groups. The graph illustrates the time-dependent effect of stress on mitochondrial function and serotonergic signaling assessed by histoenzymes. Serotonergic mediation (MAO as its indicator) has been shown to be stronger than mitochondrial enzymes CyOx and ATPase, respectively. The evaluation of the histochemical reaction was performed according to the method of Grover et al. (2015): 4 - very intense reaction; 3.5-3 - intense reaction; 2.5 - moderate reaction; 2-1 - weak reaction; 0 - negative reaction.

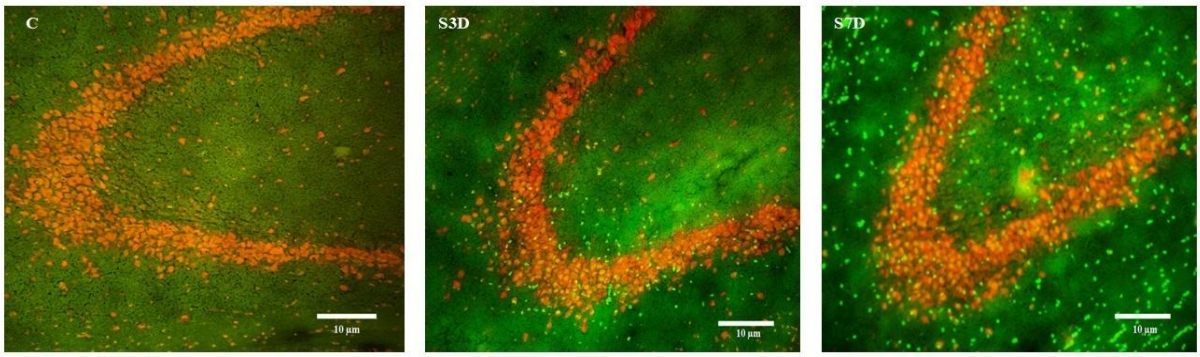


Fig. 48. Structure of hippocampal CA3 area in Control (C) and experimental groups, following the labeling of nucleic acids with acridine orange. The activation of glial cells, around the curvature of CA3 area , at a rate proportional to the time of exposure to stress is a prominent reaction. Acridineorange, x 200 (Toma et al., 2017).

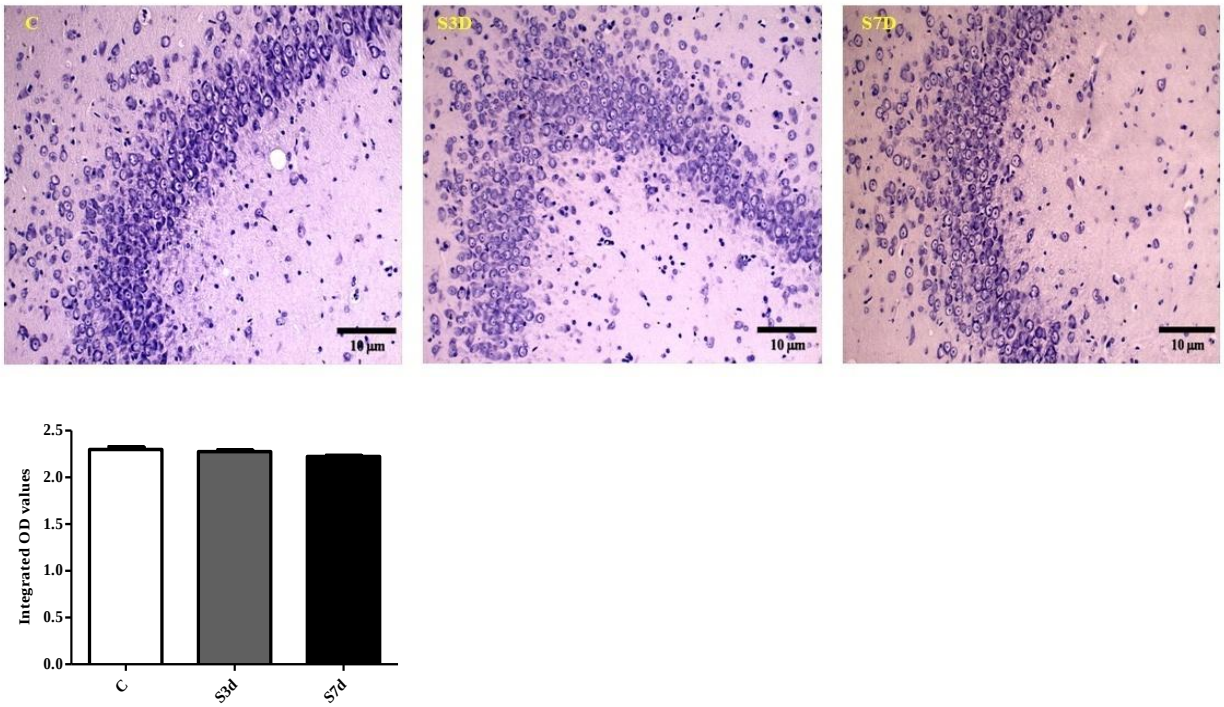


Fig. 49. Structure of the hippocampal CA3 area in Control (C) and experimental groups. Nissl staining demonstrates the absence of changes in the architecture of the area, in the neurosecretory process or in terms of neuronal morphology. The graph represents the average values of the integrated optical density for Nissl staining (blue-purple filter). The results of the integrated optical density measurement demonstrate the absence of changes in the dynamics of the Nissl substance. Nissl, x 200 (Toma et al., 2017).

8. GENERAL CONCLUSIONS

(I) The in vivo use of some prooxidant proteins, together with various molecules resulting by derivatization of Hb or Hr, revealed: (i) the exclusively humoral immune reaction, arising from exposure to Hb derivatives respectively Hr; (ii) the intersection of humoral immunity with hemostasis via platelets, fibrinogen and immunoglobulins, when the biosystem identifies blood-specific proteins; (iii) modulation of the prooxidative reactivity of Hb / Hr derivatives led to the modulation of their pathophysiological effects; (iv) there is a directly proportional relationship between oxidative stress and systemic inflammatory response.

(II) Oxidative stress, associated with neuropathologies (memory disorders, anxiety) or the modulation of the immune reaction, demonstrated the pleiomorphic character of the reactivity of the biological model used. Cerebral antioxidant activity of curcumin was observed, by modulating the NF-kβ, ERK1 / 2 and iNOS-mediated signaling pathway, after administration of a dose of diazepam (the agent that destabilized the brain redox balance).

(III) Under normal conditions, allicin played a role in stimulating B lymphocytes, via the SCAR B1 receptor, whose signaling pathway intersected with that of BCR (B Cell Receptor), leading to amplification of immunoglobulin secretion. In parallel, with the increase of immunoglobulin

synthesis and release, oxidative stress was diminished. Moreover, a series of experimental data obtained by us have shown that, there are inverse or direct proportionality relations between oxidative stress and systemic inflammatory reaction, respectively the humoral mediated immune response. The biological model, however, emphasized the multifactorial character of oxidative stress and showed that different compounds intended for various treatment schemes, act according to common laws and, at the same time, have been found to be particularly dynamic and often contradictory, of oxidative stress parameters.

(IV) Testing on the lab rat extracts of *L. album* and *L. purpureum*, under normal conditions and immobilization stress, revealed multiple protective and regulatory bioactivities thereof.

(V) The biological model used highlighted the order of entry into the defensive reaction of the model biosystem (Wistar white rat) through adaptive (i) biochemical and (ii) tissue reactions. The biological model also showed that the organs associated with the HHHS functional axis are in the first line of adaptive reaction, followed by the organs with the main metabolic role (liver, kidney). We could observe the specific bioactivity of the *L. album* extract, based on the presence in the extract of some iridoids such as SME and ASME. These iridoids were also responsible for the regenerative effects of *L. album* extract on the dentate gyrus.

(VI) In the case of in vivo tests, for the outline of the specific bioactivity, the extract of the berries showed an atypical reaction, in phytotherapy, but essential: a phytopharmaceutical preparation had no positive effects on certain organs and biochemical indicators. The biological model of ethanolic steatohepatitis and non-specific ethyl alcohol nephrotoxicity, in the white rat of the Wistar strain, revealed the pleiomorphism of a biological factor induced by a single factor, in our case, the ethanol.

(VII) The experimental data, anchored in the experimental context, have shown that the biological model used on the Wistar rat can reveal new fundamental mechanisms of action of a complex of phytocompounds (plant extract). The synergistic effect of the extract of *G. verum* with that of stress was observed, in the sense of stimulation of the adrenal glands. Overall, the results of the histological study of the hypothalamus - adenohypophysis - adrenal glands showed that the administration of *G. verum* extract, under the conditions of exposure of animals to immobilization stress, induced important morphological changes in the whole constituent assembly of the hypothalamo-pituitary-adrenal axis, the results advocating the stimulation of its secretarial activity.

(VIII) Within the biological model of non-alcoholic steatohepatitis, it could be observed that the presence of antioxidants in a plant extract does not have a priori beneficial effects, the administration matrix having a decisive role in terms of the biological effect of the extract.

(IX) It has also been noted that experimentally induced steatohepatitis with CCl_4 has been associated with increased cellular-mediated immune response and TNFα. In addition, decreasing serum hepatic marker values is not always a signal of liver regeneration. Sometimes, as in the case of our study, the decrease of the hepatic markers suggests the maximum degree of injury, as a result of which, the liver no longer has enzyme reserves that, due to fatty dystrophy and necrosis, are taken up by the local bloodstream.

(X) The biological model used to establish the anxiolytic action of *Hypericum* extracts revealed three essential issues: (i) antioxidants can have anxiolytic and antidepressant effects; (ii) the neuroimmune reaction from the anxiety disorder has been associated with increased oxidative stress; (iii) *Hypericum* extracts have adjuvant properties (we do not consider them therapeutic) in anxiolytic therapy.

(XI) In the case of the biological model used, in which, the AgNP-CM were administered under normal conditions, it was noted, as in the case of allicin studies, the structural and metabolic plasticity of the Wistar white rat. At the same time, the presence of *C. mas* compounds determined the stimulation of AgNP action revealed by the amplitude of the apoptosis and of the testicular lesions observed.

(XII) The biological model of the restraint stress, as a model for neuropsychological stress, has highlighted a new role that the hippocampus has in adapting to nitro-oxidative and neuropsychological stress. The biological model revealed a stress-buffering mechanism of the CA3 area that Wistar rat developed. In-depth studies will highlight, through the stress-buffering property, the link between the changes presented in this Doctoral Thesis and the behavioral echo of repeated exposure to stress. The biological models in which our research was carried out had as common denominator, the biology, and pathology of oxidative stress. The research was carried out using experimental models of various pathological conditions (neuropsychic stress, anxiety disorder, ethyl intoxication, steatohepatitis), or Wistar white rats with physiologically normal status (testing of Hb / Hr, allicin, curcumin derivatives). of the new mechanisms involved in the adaptation to neuropsychic stress). The convergence elements of the normal or pathological experimental models studied on the white rat of the Wistar breed, include:

(i) irrespective of the pathological status of the rat undergoing experimentation, the picture of oxidative stress varies over time;

(ii) the decrease or increase of oxidative stress is not generalized, and is strictly dependent on the experimental context;

(iii) normal biological models (without pathological condition) reflect the bioactivity of the tested molecule / compound / plant extract, in a narrower form than the tests performed with

biological models of some pathologies, where for the tested plant molecule / compound / extract, multiple implications are highlighted metabolic, structural or behavioral;

(iv) The choice of biological model is not made after the experimenter wants to obtain, but according to the specific (physical, chemical characterization, silico studies or, as the case may be, in vitro) of the molecule / compound / plant extract tested, to which certain biological effects are expected;

(v) biological models are polymorphic functional systems, which highlight the pleiomorphism of the molecule / compound / plant extract tested;

(vi) proportional to the complexity of the biological model and the analyzes performed, the researched subject is supported by multidimensional data (molecular, metabolic, morphological, interaction in signaling, behavioral pathways, etc.), and the proximity to the scientific truth is greater;

(vii) In the adaptive reaction, to certain disruptive factors, there are forms of adaptation, which we place in *adaptive-buffer forms*, capable of maintaining the redox, metabolic balance, etc. a defined period of time; after these coping buffered reactions are exhausted, the biosystem will trigger the adaptive mechanism itself (as noted in Chapter 7).

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Articles in ISI journals - as coauthor

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Brain Disord. Ther., 6(3 Suppl), 56, 2017. DOI: 10.4172/2168-975X-C1-018, (https://www.omicsonline.org/proceedings/behavior-mri-features-and-ultrastructural-bases-of-the-autism-likedisorders-induced-in-rats-by-prenatally-exposed-to-sod-80010.html).

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1) Farcas, A.D., **Toma, V.A.**, Crisan, F., Dume, B.R. & Roman, I. The down-regulation outcome of wild European apple (Malus sylvestris (L.) Mill.) extract on a series of biochemical markers during oxidative stress. *Ann. RSCB*, **22**(2), 2018, 34-41 (http://www.annalsofrscb.ro/numar%20in%20curs/22%202/farcas5.pdf)

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▪ Biological models of autism spectrum disorders: valproate, oxidative stress and development, Baru, June, 2016.

▪ Cellular and biochemical coordinates related to CA3 hippocampal field in repeated restraint stress, Oradea, June, 2016.

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▪ Coordinates of genetics of autism spectrum disorders. A review studies of the ASD-related genes in humans and lab animals, Cluj-Napoca, May, 2016.

▪ Valproic acid-induced autism spectrum disorders symptoms: theoretical, clinical and experimental coordinates, Neuroscience 2016 Virtual Conference, CA-USA, Section: Neuron Biology, March, 2016.

Hemoglobin based blood substitutes behavior in hemorrhagic conditions, Baia-Mare, June, 2015.

▪ "Artificial Blood"- Newly developed blood substitutes tested on laboratory animals and cell cultures. Preliminary results, Târgu-Mureș România, June, 2014.

RESEARCH FELLOWSHIPS

SOE Scholarship (DAAD Stipendium), Universität Leipzig 2015/2016, 6 months

World Federation of Scientist, Switzerland, 2014/2015, 12 months

Bursă de Performanţă Ştiinţifică, Universitatea Babeş-Bolyai, 2012/2013, 10 months

TRAINING COURSES

- *The Teen Brain: Insights from Neuroimaging,* Course, CME Consultants in association with LabRoots, Inc, CA, USA (2016)

- *Regulation and Function of Neurogenesis in the Adult Hippocampus,* Course, CME Consultants in association with LabRoots, Inc, CA, USA (2016)

- *The Neurobiology of Temperament and Mood,* Course, CME Consultants in association with LabRoots, Inc, CA, USA (2016)

- *Workshop in Lab Animals Medicine,* Cluj-Napoca, march, 2016.

RESEARCH PROJECTS

PN-III-P1.2-PCCDI-2017-0387 "Emerging technologies for the industrial capitalization of 2D structures (graphene and nongraphenic)" (member).

PN16-30 02 03 "Tehnologii avansate pentru producere, recuperare si stocare de energie (O1. Valorificarea potentialului de piata al rezultatelor CD din INCDTIM prin dezvoltarea de solutii inovative in domeniul energiilor alternative, tehnologiilor izotopice si al ingineriei Hi-Tech)" (member).

PN09-440.213 „ Evaluarea biochimică şi biofizică a unor proteine implicate metabolismul oxidativ, Faza I-2014/Fazele II-III-IV-2015, INCDTIM Cluj-Napoca (member).

PN 09-360.202 "Studii morfologice, fitocenologice, biochimice şi histochimice (histoenzimologice) a unor specii oficinale bogate în principii active, cu scopul obţinerii unor produse farmaceutice" Faza III/2013, Faza II/2014 Faza II-2015, INCDSB Bucureşti, ICB Cluj-Napoca (membru).

HIRSCH INDEX:

5 (la 19.03.2020) (Google Scholar)

CITATIONS

63 (Google Scholar) (la 19.03.2020)

IMPACT FACTOR:

41.795 (la 19.03.2020)

LINK GOOGLE SCHOLAR:

https://scholar.google.com/citations?user=kwF4GDUAAAAJ&hl=ro

ADMINISTRATIVE ACTIVITIES:

07.2016 - present - Council for Doctoral Studies, Babeș-Bolyai University, Institute for Doctoral Studies : member

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ACKNOWLEDGMENTS

Nihil sine Deo!

The arrival of this academic evolution and this Doctoral Thesis at this moment would not have been possible without the support of the family, who, since the age of 12, allowed me to transform the room into a biology and chemistry laboratory, inside which, way of more than 10 years, we have carried out activities so beautiful and creative. I thank the aunts for the books and the contacts offered throughout my development, with laboratories and medical institutions that inspired me. From here I thank the staff of the Clinical Laboratory of S.J.U. Bistrita, Mrs. Angela Socolean and Mr. Chem. Adrian Cop.

My teachers, only those who deserve appreciation, Geta Lăpuște, the late Leontina Rusan, Maria Pop, Luciei Nagy, Claudiei Ladar and Monicai Bojor, thank them for what they have managed to do for my academic and social development.

Acknowledgments and thanks to the collaborators of the Faculty of Biology and Geology (Lucia Boancă Techn., Anamaria Răbulea Techn., Septimiu Tripon Tech., Conf. Dr. Lucian Barbu-Tudoran, Dr. Laura Pătraș, Lecturer dr. Emilia Licărete, Lecturer dr. Alina Sesărman, Conf. dr. Manuela Banciu, Prof. dr. Doina Sandu, Acad. Prof. dr. Octavian Popescu), who trusted my ideas and made efforts for my evolution.

I thank the Department of Physiology of the UMF "Iuliu Hațieganu", Lecturer dr. Alexandra Sevastre, Assistant. dr. Ioana Bâldea and Prof. dr. Adriana Filip, with whom I have some particularly productive academic experiences. I also thank Conf. dr. Adrian Florea, for the proven openness in relation to the interpretation of the experimental data and for the sustained collaboration.

I thank Conf. Dr. Bogdan Sevastre, from USAMV Cluj-Napoca, the Discipline of Pathophysiology, who, from my early days in research, has been with me, has supported me scientifically and materially, and continues to be a close collaborator.

From the Faculty of Chemistry and Chemical Engineering of the BBU, I will have eternal gratitude for Mr. Conf. Dr. Radu Silaghi-Dumitrescu, who formed my vision on the experimental data, on the red thread of research and thanks to which, I developed several inter-institutional connections and we made the first ISI articles.

I thank Mrs. CS I, dr. Eva Fischer Fodor, from the "Ion Chiricuță" Oncology Institute from Cluj-Napoca, for the continuous dedication to my ideas and to their support.

I thank Mr. CS I Dr. Ioan Turcu from INCDTIM Cluj-Napoca for the unequivocal support of any scientific endeavor I initiated, for the appreciation he has shown towards me, as well as for the continuous material support in all these years.

I am grateful to the Romanian Society of Cell Biology, Mrs. Acad. Maya Simionescu and the late Prof. dr. Constantin Crăciun, who have identified valuable ideas, as presented by me in their congresses, over the years.

Gratitude and thanks to bringing to the Institute of Biological Research from Cluj-Napoca, the Laboratory of Animal Physiology led by Mrs. CS III dr. Ioana Roman, who from the first meeting, in the summer of 2013, showed openness and flexibility for collaboration, admirable. Thanks to this collaboration, the experiments whose results are exposed in this Doctoral Thesis were possible. In the Institute of Biological Research, we have had the most dynamic development in terms of laboratory techniques and the orientation towards a certain sub-domain of biomedical research, that of Neurobiology, Histology, and Immunohistochemistry, with a special interest in the pathology of oxidative stress with implications in neurodevelopment. I also thank Mrs. CS I dr. Sorina Fărcaș, the manager of the Institute of Biological Research from Cluj-Napoca, for the understanding given in all these years, to the Prof. dr. Nicolaie Dragoș, for the very consistent scientific discussion that we have conducted - over time as well as Mr. CS I dr. Martin Keul, for offering, 7 years ago, the first research microscope Carl-Zeiss, within the Institute of Biological Research Cluj-Napoca, with which I made the first own histological images.

Thank you colleagues, Drd. Anca Farcaș, Drd. Bogdan Țigu, Drd. Iasmina Moza, Drd. Raluca Gherman, Drd. Alexandru Farcașanu, Drd. Andrei Ștefancu, Drd. Cătălin Hădadea, Drd. Sorin Găină, Dr. Răzvan Opriș, Dr. Maxim Morariu, Bogdan Dume, Rareș Trâncă, Iuliana Petrescu, Andrei Dălălău, Veronica Isailă, Bianca Ionel, Cezara Zăgrean-Tuza, Florin Teleanu and others like them, with whom I worked or I developed discussions that inspired me.

The gratitude and thanks from me go now to Mr. Prof. dr. Marcel Pârvu, my coordinator during the doctoral studies, the one who had and has, a decisive contribution in my career orientation. Mutual trust, insight, forward thinking, bi-univocal admiration, scientific rigor, and the calm climate I was a part of, all contributed to my construction as an independent scientist.

Eius memoria numquam perdentur!